Practitioner's Docket No. JAB0828USDIV *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740) and Application for Interim Patent Term Extension Under 37 CFR 1.760

Attached hereto is an Application for Extension of Patent Term for the above-identified Patent along with (5) copies. In such Petition, Applicant provides the following sections and exhibits.

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

B. RECORDAL OF ASSIGNMENT IN PTO

II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

C. DATE OF APPROVAL (1.740(a)(3))

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5)

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

J. **STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))**

K. **ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))**

L. **FEE (1.740(a)(14))**

M. **CORRESPONDENCE**

N. **COPIES (§ MPEP 2753 (8th Edition, Rev. No. 4))**

Exhibit 1	**Merger Documents**
Exhibit 2	**Approved Labeling for INVEGA SUSTENNA™ (paliperidone palmitate) Extended-Release Injectable Suspension**
Exhibit 3	**FDA Approval Letter for INVEGA SUSTENNA™ (Paliperidone palmitate) Extended-Release Injectable Suspension**
Exhibit 4	**Copy of U.S. Patent No. 5,254,556**
Exhibit 5	**Copy of U.S. Patent & Trademark Office Maintenance Fee Statement for U.S. Patent No. 5,254,556**
Exhibit 6	**Terminal Disclaimer**
Exhibit 7	**Claims 1, 2 and 3 of U.S. Patent No. 5,254,556 Reads on the Ingredient of the Approved Product**
Exhibit 8	**DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW**
Exhibit 9	**STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED**

Date 8/6/09

Victoria Messenger
(703) 330-6011
Schellin & Associates, Ltd.
1940 Duke Street
Suite 200
Arlington, VA 22202

Practitioner's Docket No. JAB0828USDIV *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR INTERIM EXTENSION OF PATENT TERM (37 C.F.R. § 1.760)

Dear Sir:

Applicant hereby requests an Interim Patent Term Extension for a period of one (1) year as is provided under 35 U.S.C 156(e)(2) and 37 CFR 1.760.

BACKGROUND

An initial application for Interim Extension of Patent Term pursuant to 37 CFR 1.790 was filed on July 7, 2009 for US Patent 5,254,556 ('556 Patent). To applicant's knowledge the Interim Extension filed on July 7, 2009 has not been granted. The '556 Patent claims paliperidone palmitate, the active ingredient of the INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension (Product). The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

On July 31, 2009, the FDA granted a marketing authorization for the Product, which was under regulatory review under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

An Application for Patent Term Extension in compliance with 37 CFR 1.740 is being filed concurrently herewith.

The above-identified patent expires on October 27, 2009, less than three months from the date of this application for Interim Patent Term Extension.

FEE STATUS

Authorization is hereby made to charge the amount of $220.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Practitioner's Docket No. JAB0828 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556 Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G. M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. § 1.740, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for an extension of U.S. Patent No. 5,254,556 (the '556 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Hal Brent Woodrow, represent that I am a registered practitioner appointed by the patent owner of record.

B. RECORDAL OF ASSIGNMENT IN PTO

This application, U.S.S.N. 07/932,142, filed August 19, 1992, which is a Divisional of U.S.S.N. 07/422,847, filed October 17, 1989, now issued as US Patent No. 5,158,952, which is a Continuation-in-Part of U.S.S.N. 07/267,857, filed November 7, 1988, which was abandoned. An assignment of U.S.S.N. 07/422,847 was recorded: Date: November 13, 1989 at Reel/Frame: 05171/0567 847 from the named inventors to Janssen Pharmaceutica, N.V., and an assignment of U.S.S.N. 07/422,847 was recorded: Date: October 4, 2006 at Reel/Frame: 018385/0112 from Janssen Pharmaceutica, N.V. to Janssen L.P; which was dissolved by the Limited Partner, Janssen , Inc., and General Partner Janssen Pharmaceutica Inc., when they merged and subsequently became Ortho-McNeil-Janssen Pharmaceuticals, Inc. were recorded in U.S.S.N. 07/422,847: Date: May 20, 2009 at Reel/Frame: 022708/0352 (copies of the merger documents are attached as **Exhibit 1**). Additionally, US Patent No. 5,254,556 was assigned by Janssen Pharmaceutica N.V. to Ortho-McNeil-Janssen Pharmaceuticals, Inc. on July 6th, 2009 at Reel/Frame: 022915/0992. Ortho-McNeil-Janssen Pharmaceuticals, Inc. is the marketing applicant for the approved Product.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

Four additional copies of this application are attached, making a total of five copies being submitted (See§ MPEP 2753 (8th Edition).

Date: 5 August 2009

Hal Brent Woodrow

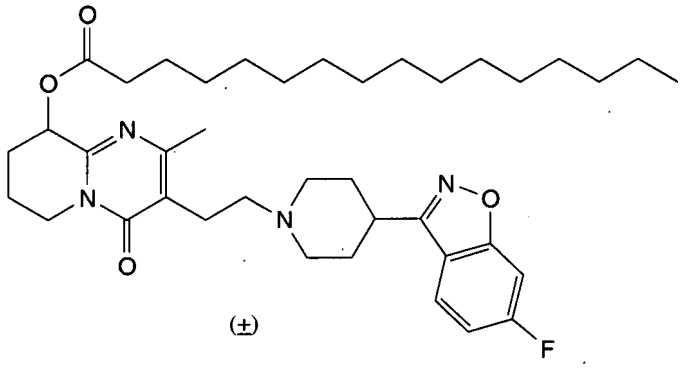
Hal Brent Woodrow
Registration No. 32501
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
USA
732-524-2976
Customer No. 27777

II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") was approved in New Drug Application ("NDA") No. 22-264 for INVEGA SUSTENNA™ (paliperidone palmitate). The active ingredient of INVEGA SUSTENNA is paliperidone palmitate. The chemical name for paliperidone palmitate is [(9RS)-3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-9-yl] hexadecanoate, also known as C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Paliperidone palmitate has the following structural formula:



B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved NDA No.22-264 for INVEGA SUSTENNA for commercial marketing or use under §505 of the FDC Act on July 31, 2009. **Exhibit 2** and **Exhibit 3**

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

INVEGA SUSTENNA is a human drug product, the sole active ingredient of which is paliperidone palmitate. Neither paliperidone palmitate, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

INVEGA™ (paliperidone) Extended Release Tablets is a human drug product, the sole active ingredient of which is paliperidone. INVEGA was approved by the FDA on December 19, 2006. Paliperidone is not a salt or ester of paliperidone palmitate.

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5))

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is September 29, 2009.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors:	Cornelus G.M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, and Jan Vandenberk
Patent No.	5,254,556
Date of Issue:	October 19, 1993
Date of Original Expiration:	October 27, 2009

A copy of the patent, including the entire specification (with claims) and drawings is attached as **Exhibit 4**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement is attached as **Exhibit 5.**

A terminal disclaimer pursuant to 37 C.F.R. §1.321(a) was filed in the '556 Patent disclaiming the terminal part of the statutory term of any patent which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154-156 and 173 of U.S. Patent No. 5,158,952. A copy of the disclaimer is attached as **Exhibit 6**. The '556 Patent is commonly owned with U.S. Patent No. 5,158,952.

No certificate of correction or reexamination certificate has issued in the '556 Patent.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '556 Patent claims the active ingredient of the Product approved which is paliperidone palmitate. The '556 Patent includes 6 claims, of which Claims 1 and 2 claim the Product, and Claim 3 claims the use of the Product.

A claim chart that lists each applicable claim of the '556 Patent and demonstrates the manner in which each claim reads on the Product is attached as **Exhibit 7.**

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '556 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was June 2, 2003 and the IND No. is 67,356.

The new drug application (NDA) was initially submitted on October 26, 2007. The NDA No. is 22-264.

The NDA was approved on July 31, 2009.

I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

Attached as **Exhibit 8** is a "DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved Product and the significant dates applicable to such activities.

J. STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

Attached as **Exhibit 9** is a "STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED" that states that in the opinion of the applicant the '556 Patent is eligible for the extension and the length of extension claimed, including how the length of extension was determined.

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Hal Brent Woodrow, the person signing below, acknowledge the applicants' duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

L. FEE (1.740(a)(14))

The Application fee due is $1,120.00 (37 C.F.R. § 1.740(a)(15) and § 1.20(j).

Authorization is hereby made to charge the amount of $1,120.00 to Deposit Account No. 10-0750/JAB0828/HBW.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750/JAB0828/HBW.

M. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Philip S. Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08816

Attn: Hal Brent Woodrow

Phone: (732) 524-2976
Facsimile: (732) 524-2808

N. COPIES (§ MPEP 2753 (8th Edition, Rev. No. 4))

Four additional copies of this application are attached, making a total of five copies being submitted.

Conclusion

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 5,254,556 is entitled to the requested 1449 day extension of its term to October 15, 2013.

Prompt action on this application is respectfully requested.

Date: 5 August 2009

Hal Brent Woodrow

Signature of Practitioner
Hal Brent Woodrow, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08816
U.S.A.

Reg. No.: 32,501
Tel. No.: 732-524-2976
Customer No.: 000027777

Exhibit 1 **Merger Documents**

'O:PHILIP S. JOHNSON COMPANY:ONE JOHNSON & JOHNSON PLAZA

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

500864728A

MAY 20, 2009

PTAS

PHILIP S. JOHNSON
ONE JOHNSON & JOHNSON PLAZA
JOHNSON & JOHNSON
NEW BRUNSWICK, NJ 08933

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 05/20/2009 REEL/FRAME: 022708/0352
NUMBER OF PAGES: 10

BRIEF: MERGER (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: JAB0650USA

ASSIGNOR:
JANSSEN, INC. THE LIMITED PARTNER OF JANSSEN, L.P. DOC DATE: 12/31/2007

ASSIGNEE:
ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC.
1125 TRENTON-HARBOURTON ROAD
TITUSVILLE, NEW JERSEY 08560

SERIAL NUMBER: 07422847 FILING DATE: 10/17/1989
PATENT NUMBER: 5158952 ISSUE DATE: 10/27/1992
TITLE: 3-[2-[4-(6-FLUORO-1,2-BENZISOXAZOL-3-YL)-1-PIPERDINYL]ETHYL]-6,7,8,9 TETRAHYDRO-9-HYDROXY-2-METHYL-4H-PYRIDO [1,2-A] PYRIMIDIN-4-ONE, COMPOSITONS AND METHOD OF USE

'O:PHILIP S. JOHNSON COMPANY:ONE JOHNSON & JOHNSON PLAZA

022708/0352 PAGE 2

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

05/20/2009
500864728

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	MERGER
EFFECTIVE DATE:	12/31/2007

CONVEYING PARTY DATA

Name	Execution Date
Janssen, Inc. the Limited Partner of Janssen, L.P.	12/31/2007

RECEIVING PARTY DATA

Name:	Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Street Address:	1125 Trenton-Harbourton Road
City:	Titusville
State/Country:	NEW JERSEY
Postal Code:	08560

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	5158952

CH $40.00 5158952

CORRESPONDENCE DATA

Fax Number: (732)524-2808
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 7816747816
Email: JNJUSPATENT@CORUS.JNJ.COM
Correspondent Name: Philip S. Johnson
Address Line 1: One Johnson & Johnson Plaza
Address Line 2: Johnson & Johnson
Address Line 4: New Brunswick, NEW JERSEY 08933

ATTORNEY DOCKET NUMBER:	JAB0650USA
NAME OF SUBMITTER:	Kristin Mele

Total Attachments: 8
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'O:PHILIP S. JOHNSON COMPANY:ONE JOHNSON & JOHNSON PLAZA

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UNITED STATES PATENT AND TRADEMARK OFFICE

Facsimile Transmission

To:	Name:	PHILIP S. JOHNSON
	Company:	ONE JOHNSON & JOHNSON PLAZA
	Fax Number:	17325242808
	Voice Phone:	
From:	Name:	ASSIGNMENT SERVICES BRANCH
	Voice Phone:	571-272-3350

37 C.F.R. 1.6 sets forth the types of correspondence that can be communicated to the Patent and Trademark Office via facsimile transmissions. Applicants are advised to use the certificate of facsimile transmission procedures when submitting a reply to a non-final or final Office action by facsimile (37 CFR 1.8(a)).

Fax Notes:

Pg#	Description
1	Cover Page
2	636.TXT
4	Document 1, Batch 1667777

USPTO ASSIGNMENT SYSTEM PROCESSING

Date and time of transmission: Wednesday, May 20, 2009 9:48:26 PM
Number of pages including this cover sheet: 05

JANSSEN, L.P.

In accordance with the Limited Partnership Agreement of Janssen, L.P., a New Jersey limited partnership, the undersigned, do hereby approve of the following:

WHEREAS, Janssen Inc. and Janssen Pharmaceutica Inc., are the limited partner and general partner, respectively, of this limited partnership,

WHEREAS, Janssen Inc. wishes to merge with and into Janssen Pharmaceutica Inc., thereby dissolving the limited partnership and filing a certificate of cancellation with the Secretary of State of New Jeresey.

NOW, THEREFORE, BE IT RESOLVED, that by virtue of the merger, this limited partnership is hereby dissolved, and further

RESOLVED, that a certificate of cancellation be and hereby is filed with the Secretary of State of New Jersey, effective as of December 31, 2007.

Janssen Inc.
Limited Partner

Douglas K. Chia, Vice President

Janssen Pharmaceutica Inc.
General Partner

Michael C. Chester, Secretary

Effective Date: December 30, 2007

CAN

FILED
DEC 2 4 2007
STATE TREASURER

0600071008

LP-103 (10/94)

New Jersey Division of Revenue
Certificate of Cancellation of a Limited Partnership
(Title NJSA 42:2A – 1 8)

1. Name of Limited Partnership:
   Janssen, L.P.
2. Limited Partnership Number:
   0600071008
3. Date of filing the Certificate of Limited Partnership:
   July 1, 1999
4. The Reasons for filing the Certificate of Cancellation are:
   The Limited Partnership no longer has assets and is no longer conducting business.
5. The effective date of this Certificate of Cancellation is December 31, 2007.

A Certificate of Cancellation must be signed by all General Partners.

Ortho-McNeil-Janssen Pharmaceuticals, Inc. (General Partner)

Signature _____ Date: 12/19/07

Signature James R. Hilton, Vice President Date:

Signature Date:

Signature Date:

Signature Date:

Signature Date:

(If more space is needed, attach an additional sheet)

S1945806
T3628712

NJ Division of Revenue, PO Box 308, Trenton, NJ 08625

COMMONWEALTH OF PENNSYLVANIA
DEPARTMENT OF STATE
CORPORATION BUREAU
206 NORTH OFFICE BUILDING
P.O. BOX 8722
HARRISBURG, PA 17105-8722
WWW.CORPORATIONS.STATE.PA.US/CORP

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

THE CORPORATION BUREAU IS HAPPY TO SEND YOU YOUR FILED DOCUMENT. THE CORPORATION BUREAU IS HERE TO SERVE YOU AND WANTS TO THANK YOU FOR DOING BUSINESS IN PENNSYLVANIA.

IF YOU HAVE ANY QUESTIONS PERTAINING TO THE CORPORATION BUREAU, PLEASE VISIT OUR WEB SITE LOCATED AT WWW.CORPORATIONS.STATE.PA.US/CORP OR PLEASE CALL OUR MAIN INFORMATION TELEPHONE NUMBER (717)787-1057. FOR ADDITIONAL INFORMATION REGARDING BUSINESS AND / OR UCC FILINGS, PLEASE VISIT OUR ONLINE "SEARCHABLE DATABASE" LOCATED ON OUR WEB SITE.

ENTITY NUMBER: 681308

CT CORPORATION SYSTEM
100 Pine Street, Suite 325
Harrisburg, PA 17101

Entity #: 681308
Date Filed: 12/18/2007
Effective Date: 12/31/2007
Pedro A. Cortés
Secretary of the Commonwealth

PENNSYLVANIA DEPARTMENT OF STATE
CORPORATION BUREAU

Articles of Amendment-Domestic Corporation

(15 Pa.C.S.)

[X] Business Corporation (§ 1915)
[ ] Nonprofit Corporation (§ 5915)

Name
Address
City State Zip Code
CT CORP-COUNTER

Document will be returned to the name and address you enter to the left.
⇐

Commonwealth of Pennsylvania
ARTICLES OF AMENDMENT-BUSINESS 3 Page(s)

T0735304123

Fee: $70

In compliance with the requirements of the applicable provisions (relating to articles of amendment), the undersigned, desiring to amend its articles, hereby states that:

1. The name of the corporation is:
Janssen Pharmaceutica Inc.

2. The (a) address of this corporation's current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a) Number and Street | City | State | Zip | County

(b) Name of Commercial Registered Office Provider | County
c/o C T Corporation System | Allegheny

3. The statute by or under which it was incorporated: Section 1306

4. The date of its incorporation: 12/18/78

5. *Check, and if appropriate complete, one of the following:*

[ ] The amendment shall be effective upon filing these Articles of Amendment in the Department of State.

[X] The amendment shall be effective on: December 31, 2007 (Date) at _____ (Hour)

DSCB:15-1915/5915-2

6. *Check one of the following:*

☐ The amendment was adopted by the shareholders or members pursuant to 15 Pa.C.S. § 1914(a) and (b) or § 5914(a).

☒ The amendment was adopted by the board of directors pursuant to 15 Pa. C.S. § 1914(c) or § 5914(b).

7. *Check, and if appropriate, complete one of the following:*

☒ The amendment adopted by the corporation, set forth in full, is as follows

That Article 1. of the Certificate of Incorporation of this Corporation be amended to read in its entirety as follows:

1. The name of the corporation is: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

☐ The amendment adopted by the corporation is set forth in full in Exhibit A attached hereto and made a part hereof.

8. *Check if the amendment restates the Articles:*

☐ The restated Articles of Incorporation supersede the original articles and all amendments thereto.

IN TESTIMONY WHEREOF, the undersigned corporation has caused these Articles of Amendment to be signed by a duly authorized officer thereof this

18 day of December, 2007.

Janssen Pharmaceutica Inc.
Name of Corporation

Signature

Eric B. Jung, Vice President
Title

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"JANSSEN INC.", A DELAWARE CORPORATION,

"MCNEIL NEWCO, INC.", A DELAWARE CORPORATION,

WITH AND INTO "ORTHO-MCNEIL PHARMACEUTICAL, INC." UNDER THE NAME OF "ORTHO-MCNEIL PHARMACEUTICAL, INC.", A CORPORATION ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF PENNSYLVANIA, AS RECEIVED AND FILED IN THIS OFFICE THE TWENTY-FIRST DAY OF DECEMBER, A.D. 2007, AT 9:54 O'CLOCK P.M.

AND I DO HEREBY FURTHER CERTIFY THAT THE EFFECTIVE DATE OF THE AFORESAID CERTIFICATE OF MERGER IS THE THIRTY-FIRST DAY OF DECEMBER, A.D. 2007.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

4479427 8100M

071357631

AUTHENTICATION: 6267570

DATE: 12-27-07

You may verify this certificate online at corp.delaware.gov/authver.shtml

State of Delaware
Secretary of State
Division of Corporations
Delivered 10:10 PM 12/21/2007
FILED 09:54 PM 12/21/2007
SRV 071357631 - 2571602 FILE

STATE OF DELAWARE
CERTIFICATE OF MERGER
DOMESTIC CORPORATION INTO
FOREIGN CORPORATION

Pursuant to Title 8, Section 252 of the Delaware General Corporation Law, the undersigned corporation executed the following Certificate of Merger:

FIRST: The name and state of incorporation of each of the constituent corporations to the merger (the "Constituent Corporations") are as follows:

Name	State of Incorporation
Janssen Inc.	Delaware
McNeil Newco, Inc.	Delaware
Ortho-McNeil-Janssen Pharmaceuticals, Inc.	Pennsylvania

SECOND: The Agreement and Plan of Merger has been approved, adopted, certified, executed and acknowledged by each of the constituent corporations pursuant to Title 8, Section 252.

THIRD: The name of the surviving corporation is Ortho-McNeil-Janssen Pharmaceuticals, Inc., a Pennsylvania corporation.

FOURTH: The Certificate of Incorporation of the surviving corporation shall be its Certificate of Incorporation.

FIFTH: The merger is to become effective on December 31, 2007.

SIXTH: The Agreement and Plan of Merger is on file at 1125 Trenton Harbourton Road, Titisville, New Jersey, 08560.

SEVENTH: A copy of the Agreement and Plan of Merger will be furnished by the surviving corporation on request, without cost, to any stockholder of the constituent corporations.

EIGHTH: The surviving corporation agrees that it may be served with process in the State of Delaware in any proceeding for enforcement of any obligation of the surviving corporation arising from this merger, including any suit or other proceeding to enforce the rights of any stockholders as determined in appraisal proceedings pursuant to the provisions of Section 262 of the Delaware General

Corporation laws, and irrevocably appoints the Secretary of State of Delaware as its agent to accept service of process in any such suit or proceeding. The Secretary of State shall mail any such process to the surviving corporation at 1125 Trenton Harbourton Road, Titusville, New Jersey 08560.

IN WITNESS WHEREOF, said surviving corporation has caused this certificate to be signed by its authorized officer, the 19th day of December, 2007.

By: _____
Authorized Officer

Name: James R. Hilton

Title: Vice President

United States Patent and Trademark Office

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Confirmation Receipt

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PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	MERGER
EFFECTIVE DATE:	12/31/2007

CONVEYING PARTY DATA

Name	Execution Date
Janssen, Inc. the Limited Partner of Janssen, L.P.	12/31/2007

RECEIVING PARTY DATA

Name:	Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Street Address:	1125 Trenton-Harbourton Road
City:	Titusville
State/Country:	NEW JERSEY
Postal Code:	08560

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	5158952

CORRESPONDENCE DATA

Fax Number: (732)524-2808
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 7816747816
Email: JNJUSPATENT@CORUS.JNJ.COM
Correspondent Name: Philip S. Johnson

Address Line 1:	One Johnson & Johnson Plaza
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Address Line 4:	New Brunswick, NEW JERSEY 08933

ATTORNEY DOCKET NUMBER:	JAB0650USA
NAME OF SUBMITTER:	Kristin Mele
Signature:	/Kristin Miele/
Date:	05/20/2009

Total Attachments: 8
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RECEIPT INFORMATION

EPAS ID:	PAT882616
Receipt Date:	05/20/2009
Fee Amount:	$40

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Exhibit 2

Approved Labeling for INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA® SUSTENNA™ safely and effectively. See full prescribing information for INVEGA® SUSTENNA™.

INVEGA® SUSTENNA™ (paliperidone palmitate) Extended-Release Injectable Suspension

Initial U.S. Approval: 2006

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA® SUSTENNA™ is not approved for use in patients with dementia-related psychosis. (5.1)

----------INDICATIONS AND USAGE----------

INVEGA® SUSTENNA™ is an atypical antipsychotic agent indicated for the acute and maintenance treatment of schizophrenia in adults (1)

----------DOSAGE AND ADMINISTRATION----------

- For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA™. (2.1)
- Initiate INVEGA® SUSTENNA™ with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 117 mg; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 mg to 234 mg based on individual patient tolerability and/or efficacy. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle. (2.1)
- Administer by intramuscular injection only, using appropriate needle sizes. For deltoid injection, use 1 ½-inch 22G needle for patients ≥ 90 kg (≥ 200 lb) or 1-inch 23G needle for patients < 90 kg (< 200 lb). For gluteal injection, use 1 ½-inch 22G needle regardless of patient weight. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Prefilled syringes containing 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg paliperidone palmitate. (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to paliperidone, risperidone, or to any components in the formulation (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). INVEGA® SUSTENNA™ is not approved for use in patients with dementia-related psychosis (5.2)
- *Neuroleptic Malignant Syndrome* : Manage with immediate discontinuation of drug and close monitoring (5.3)
- *QT Prolongation:* increase in QT interval, avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- *Tardive Dyskinesia*: Discontinue drug if clinically appropriate (5.5)
- *Hyperglycemia and Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.6)
- *Weight Gain:* Significant weight gain has been reported. Monitor weight gain (5.7)
- *Hyperprolactinemia:* Prolactin elevations occur and persist during chronic administration (5.8)
- *Orthostatic Hypotension and Syncope*: Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.9)
- *Leukopenia, Neutropenia, and Agranulocytosis*: has been reported with antipsychotics, including INVEGA®, an oral form of paliperidone. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® SUSTENNA™ should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.10)
- *Potential for Cognitive and Motor Impairment* : Use caution when operating machinery (5.11)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)
- *Suicide*: Closely supervise high-risk patients (5.14)
- *Administration*: For intramuscular injection only. Avoid inadvertent injection into a blood vessel (5.18)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Centrally-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol. (7.1)
- Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with INVEGA® SUSTENNA™. (7.1)
- Co-administration of oral paliperidone extended release with carbamazepine decreased mean steady-state Cmax and AUC of paliperidone by approximately 37%. Adjust dose of INVEGA® SUSTENNA™ if necessary. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Renal impairment: INVEGA® SUSTENNA™ has not been systematically studied in patients with renal impairment. For mild renal impairment (creatinine clearance ≥50 mL/min to < 80 mL/min), administer 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg. in either the deltoid or gluteal muscle. INVEGA® SUSTENNA™ is not recommended for use in patients with moderate to severe renal impairment (creatinine clearance <50 mL/min). (2.5)
- Elderly: same as for younger adults (adjust dose according to renal function status). (2.5)
- Nursing Mothers: should not breast feed. (8.3)
- Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [INSERT MM/YYYY OF FDA APPROVAL]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis. ***[See Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

INVEGA® SUSTENNA™ (paliperidone palmitate) is indicated for the acute and maintenance treatment of schizophrenia in adults *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA™.

Recommended initiation of INVEGA® SUSTENNA™ is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 117 mg; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 to 234 mg based on individual patient tolerability and/or efficacy. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA® SUSTENNA™ should be considered *[see Clinical Pharmacology (12.3)]*, as the full effect of the dose adjustment may not be evident for several months.

2.2 Missed Doses

Avoiding Missed Doses

It is recommended that the second initiation dose of INVEGA® SUSTENNA™ be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week timepoint. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly timepoint.

Missed Dose (1 Month to 6 Weeks)

After initiation, the recommended injection cycle of INVEGA® SUSTENNA™ is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed Dose (> 6 Weeks to 6 Months)

If more than 6 weeks have elapsed since the last injection of INVEGA® SUSTENNA™, **resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first two injections should each be 156 mg)** in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection (same dose) one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

Missed Dose (> 6 Months)

If more than 6 months have elapsed since the last injection of INVEGA® SUSTENNA™, initiate dosing as described in Section 2.1 above.

2.3 Administration Instructions

INVEGA® SUSTENNA™ is intended for intramuscular use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

The recommended needle size for administration of INVEGA® SUSTENNA™ into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg (≥ 200 lb), the 1½-inch, 22-gauge needle is recommended. For those < 90 kg (< 200 lb), the 1-inch, 23 gauge needle is recommended. Deltoid injections should be alternated between the two deltoid muscles.

The recommended needle size for administration of INVEGA® SUSTENNA™ into the gluteal muscle is the 1½-inch, 22 gauge needle. Administration should be made into the upper-outer

quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

2.4 Use with Oral Paliperidone or with Risperidone

Concomitant use of INVEGA® SUSTENNA™ with oral paliperidone or oral or injectable risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if any of these medications are coadministered with INVEGA® SUSTENNA™.

2.5 Dosage in Special Populations

Renal Impairment

INVEGA® SUSTENNA™ has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), recommended initiation of INVEGA® SUSTENNA™ is with a dose of 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle.

INVEGA® SUSTENNA™ is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Hepatic Impairment

INVEGA® SUSTENNA™ has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment. *[See Clinical Pharmacology (12.3)]*

Elderly

In general, recommended dosing of INVEGA® SUSTENNA™ for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. As elderly patients may have reduced renal function, see *Renal Impairment* above for dosing recommendations in patients with renal impairment.

2.6 Maintenance Therapy

INVEGA® SUSTENNA™ has been shown to be effective in delaying time to relapse of symptoms of schizophrenia in long-term use. It is recommended that responding patients be continued on treatment at the lowest dose needed. Patients should be periodically reassessed to determine the need for continued treatment.

2.7 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to INVEGA® SUSTENNA™, or concerning concomitant administration with other antipsychotics.

Switching from Oral Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA™.

Previous oral antipsychotics can be discontinued at the time of initiation of treatment with INVEGA® SUSTENNA™. INVEGA ® SUSTENNA ™ should be initiated as described in Section 2.1. Patients previously stabilized on different doses of INVEGA® Extended-Release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA ® SUSTENNA ™ monthly doses as depicted in Table 1.

Table 1. Doses of INVEGA® and INVEGA® SUSTENNA™ needed to attain similar paliperidone exposure at steady-state

Formulation	INVEGA® Extended-Release Tablet	INVEGA® SUSTENNA™ Injection
Dosing Frequency	Once Daily	Once every 4 weeks
Dose (mg)	12 6 3	234 117 39-78

Switching from Long-Acting Injectable Antipsychotics

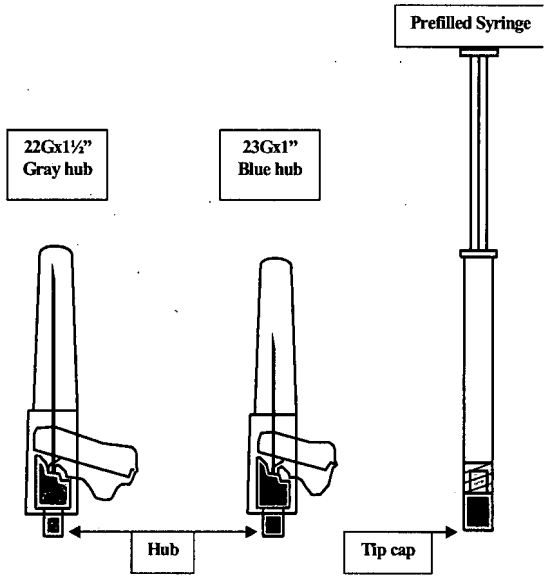
For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA™.

When switching patients from previous long-acting injectable antipsychotics, initiate INVEGA® SUSTENNA™ therapy in place of the next scheduled injection. INVEGA® SUSTENNA™ should then be continued at monthly intervals. The one-week initiation dosing regimen as described in Section 2.1 is not required.

If INVEGA® SUSTENNA™ is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

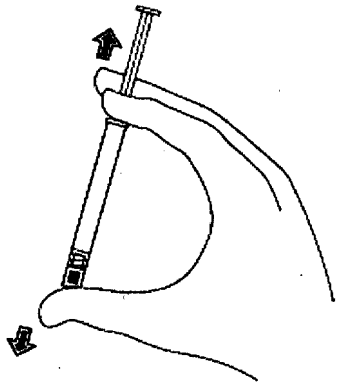
2.8 Instructions for Use

The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.



INVEGA® SUSTENNA™ is for single use only.

1. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.

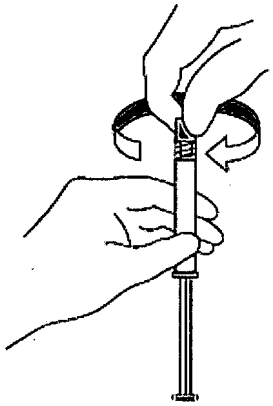


2. Select the appropriate needle.

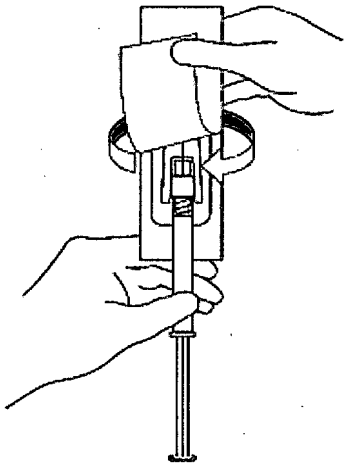
   For DELTOID injection, if the patient weighs < 200 lb (< 90 kg), use the 1-inch **23** gauge needle (needle with **blue** colored hub); if the patient weighs ≥ 200 lb (≥ 90 kg), use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

   For GLUTEAL injection, use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

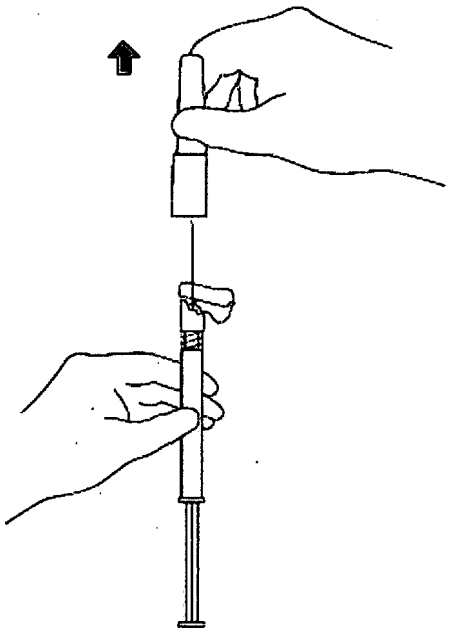
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



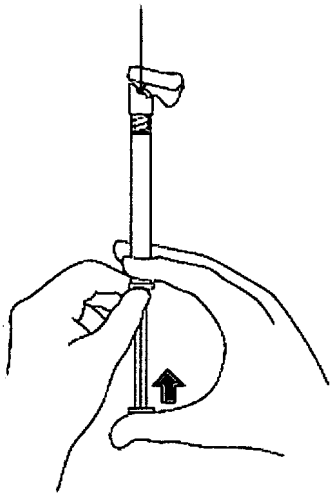
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



5. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.



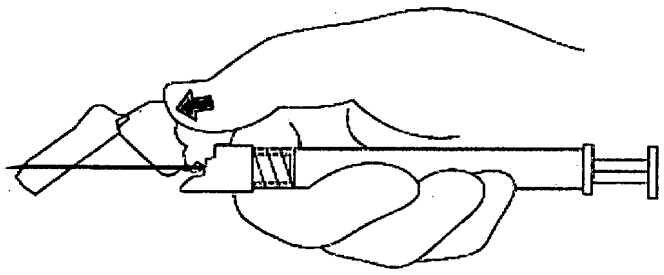
6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.



7. Inject the entire contents intramuscularly into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**

8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle protection system. The needle protection system is fully activated when a 'click' is heard. Discard the syringe with needle appropriately.

8a



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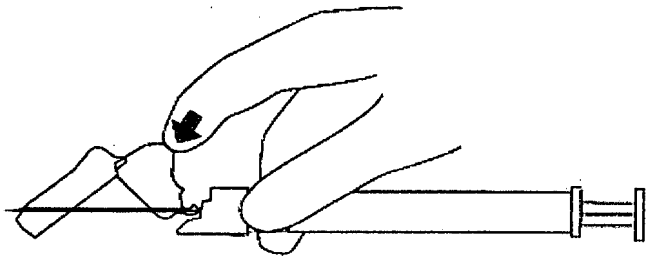
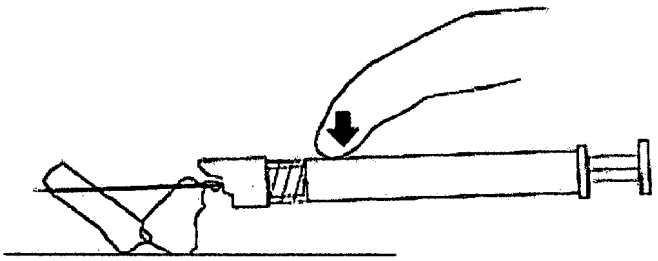


8c



3 DOSAGE FORMS AND STRENGTHS

INVEGA® SUSTENNA™ is available as a white to off-white aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate.

4 CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA® SUSTENNA™ formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of dementia-related psychosis ***[see Boxed Warning].***

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Oral paliperidone and INVEGA® SUSTENNA™ were not marketed at the time these studies were performed and are not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated

extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA® SUSTENNA™ administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which

$C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA® SUSTENNA™, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® SUSTENNA™ should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA®

SUSTENNA™, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® SUSTENNA™ despite the presence of the syndrome.

5.6 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA® SUSTENNA™. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.7 Weight Gain

Weight gain has been observed with INVEGA® SUSTENNA™ and other atypical antipsychotics. In the 13-week study involving 234 mg initiation dosing, the proportion of subjects with an abnormal weight increase $\geq$ 7% showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA® SUSTENNA™ 39 mg, 156 mg, and 234 mg groups, respectively. In the two 13-week, fixed-dose, double-blind, placebo-controlled trials (pooled data), the proportions of subjects meeting a weight gain criterion of $\geq$ 7% of body weight were 6%, 9%, and 10% in the INVEGA® SUSTENNA™ 39 mg, 78 mg, and 156 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, 8% and 6% in

the INVEGA® SUSTENNA™ 78 mg and 156 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label period (9-week flexible-dose transition phase followed by a 24 week maintenance phase flexible-dose and minimum 12-week fixed dose) of the maintenance trial, 12% of INVEGA® SUSTENNA™-treated subjects met this criterion; the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion (weight gain of ≥ 7% from double-blind phase to endpoint) was met by 6% of INVEGA® SUSTENNA™-treated subjects compared with 3% of placebo-treated subjects; the mean weight change from double-blind baseline was +0.5 kg for INVEGA® SUSTENNA™ compared with –1.0 kg for placebo. Similar results were observed in the open-label extension phase of this study.

5.8 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

5.9 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with

INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA® SUSTENNA™-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies were similar to those observed in the short-term studies.

INVEGA® SUSTENNA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.10 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including INVEGA®, an oral form of paliperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® SUSTENNA™ should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® SUSTENNA™ and have their WBC followed until recovery.

5.11 Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA® SUSTENNA™ *[see Adverse Reactions (6.1)]*. Antipsychotics, including INVEGA® SUSTENNA™, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.12 Seizures

In the four fixed-dose double-blind placebo-controlled studies, <1% (1/1293) of subjects treated with INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA® SUSTENNA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA® SUSTENNA™ and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.14 Suicide

The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy.

5.15 Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA® SUSTENNA™, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

5.16 Thrombotic Thrombocytopenic Purpura (TTP)

No cases of TTP were observed during clinical studies with oral paliperidone or INVEGA® SUSTENNA™. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

5.17 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA® SUSTENNA™ to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.18 Administration

INVEGA® SUSTENNA™ is intended for intramuscular injection, and care must be taken to avoid inadvertent injection into a blood vessel *[see Dosage and Administration (2.3)]*.

5.19 Antiemetic Effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

5.20 Use in Patients with Concomitant Illness

Clinical experience with INVEGA® SUSTENNA™ in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA® SUSTENNA™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA® SUSTENNA™, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions (5.9)]*.

5.21 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions (5.6)]*
- Weight Gain *[see Warnings and Precautions (5.7)]*

- Hyperprolactinemia *[see Warnings and Precautions (5.8)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.9)]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.10)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Suicide *[see Warnings and Precautions (5.14)]*
- Priapism *[see Warnings and Precautions (5.15)]*
- Thrombotic Thrombocytopenic Purpura *[see Warnings and Precautions (5.16)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.17)]*
- Avoidance of inadvertent injection into a blood vessel *[see Warnings and Precautions (5.18)]*
- Antiemetic effect *[see Warnings and Precautions (5.19)]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions (5.20)]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions (5.20)]*

Throughout this section, a distinction is made between adverse events and adverse reactions. Adverse events are events reported by the clinician investigator and there is no attempt to assign causality to the study drug. Adverse reactions are adverse events that are considered to be reasonably associated with the use of INVEGA® SUSTENNA™ (adverse drug reactions) based on a predetermined method of assessment, e.g., a comparison of adverse event rates for drug and placebo groups for the event of interest. It is not possible to reliably establish causality by considering individual adverse event reports for drug-treated patients. Thus, the section overall is labeled Adverse Reactions, however, individual subsections are labeled adverse reactions or adverse events, depending on what is included in the subsection.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common (at least 5% in any INVEGA® SUSTENNA™ group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder.

The data described in this section are derived from a clinical trial database (Phase 2 and 3) consisting of a total of 2770 subjects with schizophrenia who received at least one dose of INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 2770 INVEGA® SUSTENNA™-treated subjects, 1293 received INVEGA® SUSTENNA™ in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA® SUSTENNA™ in the maintenance trial (of whom 205 continued to receive INVEGA® SUSTENNA™ during the double-blind placebo-controlled phase of this study), and 628 received INVEGA® SUSTENNA™ in two non-placebo controlled trials (a noninferiority active-comparator trial and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA® SUSTENNA™ initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The majority of all adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Events in Double-Blind, Placebo-Controlled Clinical Trials

Table 2 lists the adverse events reported in 2% or more of INVEGA® SUSTENNA™-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

Table 2. Incidence of Treatment Emergent Adverse Events in ≥ 2% of INVEGA® SUSTENNA™-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

System Organ Class Adverse Event	**Placebo[a] (N=510)**	**39 mg (N=130)**	**78 mg (N=302)**	**156 mg (N=312)**	**234/39 mg[b] (N=160)**	**234/156 mg[b] (N=165)**	**234/234 mg[b] (N=163)**
Total percentage of subjects with adverse event	70	75	68	69	63	60	63
Gastrointestinal disorders							
Abdominal discomfort/abdominal	1	0	3	3	1	2	3

pain upper							
Constipation	5	3	5	5	2	4	1
Diarrhea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reactions	2	0	4	6	9	7	10
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Injury, poisoning and procedural complications							
Skin laceration	<1	2	<1	0	1	0	0
Investigations							
Alanine aminotransferase increased	2	0	2	1	1	1	1
Weight increased	1	4	4	1	1	1	2
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Insomnia	15	15	15	13	12	10	13
Nightmare	<1	2	0	0	0	0	0
Suicidal ideation	2	0	1	2	2	2	1
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

Percentages are rounded to whole numbers. Table includes adverse events that were reported in 2% or more of subjects in any of the INVEGA® SUSTENNA™ dose groups and which occurred at greater incidence than in the placebo group.

[a] Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design.

[b] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[See Clinical Studies (14)]*

Adverse events for which the paliperidone palmitate incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain upper, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse events were collapsed and are grouped under "Injection site reactions".

6.2 Other Adverse Reactions Observed During the Premarketing Evaluation of INVEGA® SUSTENNA™ Not Listed in Table 2

The following additional adverse reactions occurred in INVEGA® SUSTENNA™-treated subjects in the above four fixed-dose, double-blind, placebo-controlled trials, in the double-blind phase of the maintenance trial, or in INVEGA® SUSTENNA™-treated subjects with schizophrenia who participated in other Phase 3 trials, and were not reported in Table 2. They were determined to be adverse reactions based upon reasons to suspect causality such as timing of onset or termination with respect to drug use, plausibility in light of the drug's known pharmacology, occurrence at a frequency above that expected in the treated population or occurrence of an event typical of drug-induced adverse reactions.

Cardiac disorders: bradycardia, bundle branch block, postural orthostatic tachycardia syndrome, tachycardia

Ear and labyrinth disorders: vertigo

Endocrine disorders: hyperprolactinemia

Eye disorders: oculogyric crisis, eye rolling, vision blurred

Gastrointestinal disorders: salivary hypersecretion, stomach discomfort

Investigations: blood cholesterol increased, blood glucose increased

Metabolism and nutrition disorders: decreased appetite, increased appetite

Nervous system disorders: convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, neuroleptic malignant syndrome, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: restlessness

Reproductive system and breast disorders: amenorrhea, erectile dysfunction, galactorrhea, gynecomastia, menstruation irregular, sexual dysfunction

Skin and subcutaneous tissue disorders: pruritus generalized, rash

Vascular disorders: orthostatic hypotension

6.3 Discontinuations Due to Adverse Events

The percentages of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled trials were 5.0% and 7.8% in INVEGA® SUSTENNA™- and placebo-treated subjects, respectively.

6.4 Dose-Related Adverse Reactions

Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials, among the adverse reactions that occurred at ≥ 2% incidence in the subjects treated with INVEGA® SUSTENNA™, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA® SUSTENNA™-treated subjects from the four fixed-dose studies.

6. 5 Demographic Differences

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects ≥ 65 years of age.

6.6 Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline or score at the end of trial) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, (4) the Abnormal Involuntary Movement Scale scores (mean change from baseline or scores at the end of trial) *(Table 3)*, and (5) incidence of spontaneous reports of EPS *(Table 4)*.

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication

	Percentage of Subjects			
		INVEGA® SUSTENNA™		
Scale	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Parkinsonism[a]	9	12	10	6
Akathisia[b]	5	5	6	5
Dyskinesia[c]	3	4	6	4
Use of Anticholinergic Medications[d]	12	10	12	11

a: For Parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)

b: For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint

c: For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint

d: Percent of subjects who received anticholinergic medications to treat emergent EPS

Table 4. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term

	Percentage of Subjects			
		INVEGA® SUSTENNA™		
EPS Group	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism	5	6	6	4
Hyperkinesia	2	2	2	4
Tremor	3	2	2	3
Dyskinesia	1	2	3	1
Dystonia	0	1	1	2

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of Parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA® SUSTENNA™ 156 mg group (18% and 11%, respectively) than in the INVEGA® SUSTENNA™ 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study involving 234 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA® SUSTENNA™ 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the

placebo (4.9%) and INVEGA® SUSTENNA™ 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

6.7 Laboratory Test Abnormalities

In the pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials, a between-group comparison revealed no medically important differences between INVEGA® SUSTENNA™ and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® SUSTENNA™ and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® SUSTENNA™ was associated with increases in serum prolactin *[see Warnings and Precautions (5.8)]*. The results from the 13-week study involving 234 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the maintenance trial exhibited comparable findings.

6.8 Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

In the 13-week study involving 234 mg initiation dosing, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA® SUSTENNA™ and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA® SUSTENNA™ groups.

Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA® SUSTENNA™ and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA® SUSTENNA™ and placebo groups.

6.9 Adverse Reactions Reported With Oral Paliperidone

The following is a list of additional adverse reactions that have been reported with oral paliperidone in subjects with schizophrenia:

Cardiac disorders: atrioventricular block first degree, palpitations, sinus arrhythmia

Gastrointestinal disorders: abdominal pain, swollen tongue

General disorders and administration site conditions: edema

Immune system disorders: anaphylactic reaction

Musculoskeletal and connective tissue disorders: muscle rigidity

Nervous system disorders: tremor

Reproductive system and breast disorders: priapism, breast discharge

Vascular disorders: ischemia

6.10 Adverse Reactions Reported With Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the ADVERSE REACTIONS sections of the package inserts for those products.

7 DRUG INTERACTIONS

Since paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

7.1 Potential for INVEGA® SUSTENNA™ to Affect Other Drugs

Given the primary CNS effects of paliperidone *[see Adverse Reactions (6.1)]*, INVEGA® SUSTENNA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA® SUSTENNA™ is administered with other therapeutic agents that have this

potential *[see Warnings and Precautions (5.9)]*.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

7.2 Potential for Other Drugs to Affect INVEGA® SUSTENNA™

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA® SUSTENNA™ should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® SUSTENNA™ should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology (12.3)]*. In an interaction study in healthy subjects in which a single 3 mg dose of oral paliperidone extended release was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

Co-administration of a single dose of an oral paliperidone extended-release 12 mg tablet with divalproex sodium extended-release tablets (two 500 mg tablets once daily at steady-state)

resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Although this interaction has not been studied with INVEGA® SUSTENNA™, a clinically significant interaction would not be expected between divalproex sodium and INVEGA® SUSTENNA™ intramuscular injection.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 250 mg /kg, which is 10 times the maximum recommended human 234 mg dose of INVEGA® SUSTENNA™ on a mg/m^2 basis.

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human dose [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see RISPERDAL® package insert).

There are no adequate and well controlled studies of INVEGA® SUSTENNA™ in pregnant women. INVEGA® SUSTENNA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

8.2 Labor and Delivery

The effect of INVEGA® SUSTENNA™ on labor and delivery in humans is unknown.

8.3 Nursing Mothers

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA® SUSTENNA™ should not breast feed infants.

8.4 Pediatric Use

Safety and effectiveness of INVEGA® SUSTENNA™ in patients < 18 years of age have not been established.

8.5 Geriatric Use

Clinical studies of INVEGA® SUSTENNA™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment *[see Clinical Pharmacology (12.3)]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5)]*.

8.6 Renal Impairment

INVEGA® SUSTENNA™ has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), recommended initiation of INVEGA® SUSTENNA™ is with a dose of 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle.

INVEGA® SUSTENNA™ is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

8.7 Hepatic Impairment

INVEGA® SUSTENNA™ has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA® SUSTENNA™ (paliperidone) is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

9.3 Dependence

Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

No cases of overdose were reported in premarketing studies with INVEGA® SUSTENNA™. Because INVEGA® SUSTENNA™ is to be administered by health care professionals, the potential for overdosage by patients is low.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

10.2 Management of Overdosage

There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the prolonged-release characteristics of INVEGA® SUSTENNA™ and the long apparent half-life of paliperidone when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

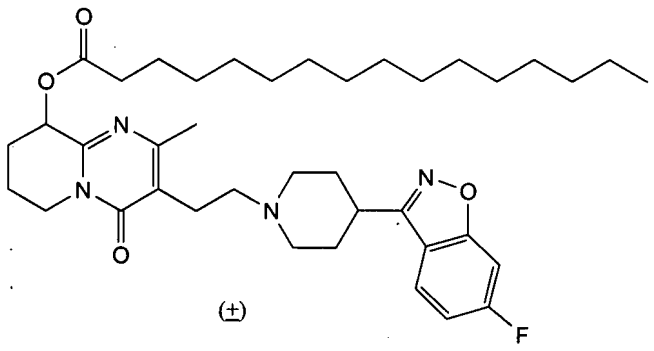
Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone.

Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

11 DESCRIPTION

INVEGA® SUSTENNA™ contains paliperidone palmitate. The active ingredient, paliperidone palmitate, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. INVEGA® SUSTENNA™ contains a racemic mixture of (+)- and (-)- paliperidone palmitate. The chemical name is (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimadin-9-yl hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



(±)

Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.

INVEGA® SUSTENNA™ is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

INVEGA® SUSTENNA™ is provided in a prefilled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The kit also contains 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D_2) receptor antagonist and a serotonin Type 2 ($5HT_{2A}$) receptor antagonist. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro*.

12.3 Pharmacokinetics

Absorption and Distribution

Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 13 days. The release of the drug starts as early as day 1 and lasts for as long as 126 days.

Following intramuscular injection of single doses (39 mg - 234 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 234 mg on day 1 and 156 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA® SUSTENNA™ results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA® SUSTENNA™ administration was dose-proportional over a 39 mg - 234 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 78 mg . The mean steady-state peak:trough ratio for a INVEGA® SUSTENNA™ dose of 156 mg was 1.8 following gluteal administration and 2.2 following deltoid administration.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6–1.8.

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

In a study with oral immediate-release ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernable difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

The median apparent half-life of paliperidone following INVEGA® SUSTENNA™ single-dose administration over the dose range of 39 mg - 234 mg ranged from 25 days - 49 days.

Long-Acting Paliperidone Palmitate Injection versus Oral Extended-Release Paliperidone

INVEGA® SUSTENNA™ is designed to deliver paliperidone over a monthly period while extended-release oral paliperidone is administered on a daily basis. The initiation regimen for INVEGA® SUSTENNA™ (234 mg/156 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

In general, overall initiation plasma levels with INVEGA® SUSTENNA™ were within the exposure range observed with 6-12 mg extended-release oral paliperidone. The use of the INVEGA® SUSTENNA™ initiation regimen allowed patients to stay in this exposure window

of 6-12 mg extended-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from INVEGA® SUSTENNA™ was lower relative to the variability determined from extended-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Special Populations

Renal Impairment

INVEGA® SUSTENNA™ has not been systematically studied in patients with renal impairment. Based on a limited number of observations with INVEGA® SUSTENNA™ in subjects with mild renal impairment and pharmacokinetic simulations, the dose of INVEGA® SUSTENNA™ should be reduced in patients with mild renal impairment; INVEGA® SUSTENNA™ is not recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.5)]*. Although INVEGA® SUSTENNA™ was not studied in patients with moderate or severe renal impairment, the disposition of a single oral dose paliperidone 3 mg extended-release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 mL/min to < 80 mL/min), 64% in moderate (CrCl = 30 mL/min to < 50 mL/min), and 71% in severe (CrCl = 10 mL/min to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5 fold, 2.6 fold, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA® SUSTENNA™ in subjects with mild renal impairment and pharmacokinetic simulations, the recommended initiation of INVEGA® SUSTENNA™ for patients with mild renal impairment is with a dose of 156 mg, on treatment day 1 and 117 mg on treatment day 8; thereafter, follow with monthly injections of 78 mg *[see Dosage and Administration (2.5)]*.

Hepatic Impairment

INVEGA® SUSTENNA™ has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh Class B), no dose adjustment is required in patients with mild or moderate hepatic impairment *[see Dosage and Administration (2.5)]*. In the study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Paliperidone has not been studied in patients with severe hepatic impairment.

Elderly

No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance *[see Renal Impairment above and Dosage and Administration (2.5)]*.

Race

No dosage adjustment is recommended based on race. No differences in pharmacokinetics were observed between Japanese and Caucasians.

Gender

No dosage adjustment is recommended based on gender, although slower absorption was observed in females in a population pharmacokinetic analysis.

Smoking

No dosage adjustment is recommended based on smoking status. Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg /kg/month, which is 0.6, 2, and 4 times, respectively, the maximum recommended human 234 mg dose of INVEGA® SUSTENNA™ on a mg/m^2 basis. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 47 mg and 94 mg /kg/month. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone on a mg/m^2 basis (see RISPERDAL® package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2-receptor antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown *[see Warnings*

and Precautions (5.8)].

Mutagenesis

Paliperidone palmitate showed no genotoxic potential in the Ames reverse mutation test or the mouse lymphoma assay. No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test.

Impairment of Fertility

Fertility studies of paliperidone palmitate have not been performed.

In a study of fertility conducted with orally administered paliperidone, the percentage of treated female rats that became pregnant was not affected at doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss were increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose (12 mg/day) of orally administered paliperidone (INVEGA®) on a mg/m^2 basis.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

14 CLINICAL STUDIES

The efficacy of INVEGA® SUSTENNA™ in the acute treatment of schizophrenia was evaluated in four short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia. The fixed doses of INVEGA® SUSTENNA™ in these studies were given on days 1, 8, and 36 in the 9-week study, and additionally on day 64 of the 13-week studies, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression.

In a 13-week study (n=636) comparing three fixed doses of INVEGA® SUSTENNA™ (initial deltoid injection of 234 mg followed by 3 gluteal or deltoid doses of either 39 mg/4 weeks, 156 mg/4 weeks or 234 mg/4 weeks) to placebo, all three doses of INVEGA® SUSTENNA™ were superior to placebo in improving the PANSS total score.

In another 13-week study (n=349) comparing three fixed doses of INVEGA® SUSTENNA™ (78 mg/4 weeks, 156 mg/4 weeks, and 234 mg/4 weeks) to placebo, only 156 mg/4 weeks of INVEGA® SUSTENNA™ was superior to placebo in improving the PANSS total score.

In a third 13-week study (n=513) comparing three fixed doses of INVEGA® SUSTENNA™ (39 mg/4 weeks, 78 mg/4 weeks, and 156 mg/4 weeks) to placebo, all three doses of INVEGA® SUSTENNA™ were superior to placebo in improving the PANSS total score.

In the 9-week study (n=197) comparing two fixed doses of INVEGA® SUSTENNA™ (78 mg/4 weeks and 156 mg/4 weeks) to placebo, both doses of INVEGA® SUSTENNA™ were superior to placebo in improving PANSS total score.

The efficacy of INVEGA® SUSTENNA™ in maintaining symptomatic control in schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia. This study included a minimum 12-week fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of INVEGA® SUSTENNA™ they received during the stabilization phase, i.e., 39 mg, 78 mg, or 156 mg administered every 4 weeks, or to placebo. A total of 410 stabilized patients were randomized to either INVEGA® SUSTENNA™ or to placebo until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness). The primary efficacy variable was time to relapse. A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA® SUSTENNA™ compared to placebo, and the study was stopped early because maintenance of efficacy was demonstrated.

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA® SUSTENNA™ is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

39 mg paliperidone palmitate kit (NDC 50458-560-01)

78 mg paliperidone palmitate kit (NDC 50458-561-01)

117 mg paliperidone palmitate kit (NDC 50458-562-01)

156 mg paliperidone palmitate kit (NDC 50458-563-01)

234 mg paliperidone palmitate kit (NDC 50458-564-01)

Storage and Handling

Store at room temperature (25°C, 77°F); excursions between 15°C and 30°C (between 59°F and 86°F) are permitted.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA® SUSTENNA™. See FDA-approved patient labeling.

17.1 Orthostatic Hypotension

Patients should be advised that there is risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.9)]*.

17.2 Interference with Cognitive and Motor Performance

As INVEGA® SUSTENNA™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA® SUSTENNA™ therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

17.3 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA® SUSTENNA™ *[see Use in Specific Populations (8.1)]*.

17.4 Nursing

Patients should be advised not to breast-feed an infant during treatment with INVEGA® SUSTENNA™ *[see Use in Specific Populations (8.3)]*.

17.5 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions *[see Drug Interactions (7)]*.

17.6 Alcohol

Patients should be advised to avoid alcohol while taking INVEGA® SUSTENNA™ *[see Drug Interactions (7.1)]*.

17.7 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.17)]*.

INVEGA® SUSTENNA™ (paliperidone palmitate) Extended-Release Injectable Suspension

Manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

Manufactured for:
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Revised: [Month YYYY]

Information for Patients and Caregivers

INVEGA® SUSTENNA™ (paliperidone palmitate)
Extended-Release Injectable Suspension

Important Information

This summary contains important information about INVEGA® SUSTENNA™ for patients and caregivers and has been reviewed by the U.S. Food and Drug Administration.

Read this information carefully and talk to your doctor or treatment team if you have any questions about INVEGA® SUSTENNA™. Keep this information handy so that you can refer to it later if you have any questions. Ask your doctor or treatment team if there is any new information that you need to know about INVEGA® SUSTENNA™.

This summary does not contain all the information about INVEGA® SUSTENNA™. It does not take the place of talking with your doctor.

What is INVEGA® SUSTENNA™?

INVEGA® SUSTENNA™ is a type of prescription medicine called an atypical antipsychotic given as an injection by a healthcare provider.

INVEGA® SUSTENNA™ is used to treat symptoms of schizophrenia. INVEGA® SUSTENNA™ can also be used to lessen the chance of your schizophrenia symptoms from coming back.

How does INVEGA® SUSTENNA™ work?

Schizophrenia is believed to be caused when certain chemicals in the brain are not in balance. Not all people with schizophrenia have the same symptoms. Some of the most common symptoms of schizophrenia may include:

- Seeing, hearing, or sensing things that are not there (hallucinations)
- Believing that what other people say are not true (delusions)
- Not trusting others and feeling very suspicious (paranoia)
- Avoiding family and friends and wanting to be alone

The exact way INVEGA® SUSTENNA™ works is not known. INVEGA® SUSTENNA™ is thought to help restore the balance of these chemicals in the brain, and has been shown to help many people manage their symptoms of schizophrenia.

It may take some time before your symptoms of schizophrenia start to improve. Remember that INVEGA® SUSTENNA™ is one part of your overall treatment plan. It is important to keep all your appointments so you can get your treatments on time and your treatment team can check your progress.

What is the most important safety information I need to know about INVEGA® SUSTENNA™?

INVEGA® SUSTENNA™ is not approved for the treatment of dementia-related psychosis in elderly patients. Elderly patients who were given oral antipsychotics like INVEGA® SUSTENNA™ in clinical studies for psychosis caused by dementia (memory problems) had a higher risk of death.

Who should not use INVEGA® SUSTENNA™?

INVEGA® SUSTENNA™ is not approved for the treatment of elderly patients who have a diagnosis of psychosis related to dementia.

Do not take INVEGA® SUSTENNA™ if you:

- Are allergic to paliperidone (INVEGA™ Extended-release Tablets) or any other ingredient in INVEGA® SUSTENNA™. Ask your doctor or pharmacist for a list of these ingredients.
- Are allergic to risperidone (RISPERDAL®).

What should I tell my doctor before starting INVEGA® SUSTENNA™?

Only your doctor can decide if INVEGA® SUSTENNA™ is right for you. Before you start INVEGA® SUSTENNA™, be sure to tell your doctor or treatment team if you:

- Have a history of heart problems, any problems with the way your heart beats, or are being treated for high blood pressure.
- Have diabetes or a family history of diabetes.
- Have a history of low white blood cell counts.
- Have low levels of potassium or magnesium in your blood.
- Are being treated for seizures (fits or convulsions), have had seizures in the past, or have conditions that increase the risk of having seizures.
- Have kidney or liver problems.
- Have ever had any conditions that cause dizziness or fainting.
- Are pregnant or plan to become pregnant during treatment.
- Are breast-feeding. Women should not breast-feed a baby during treatment.

- Are taking or plan to take any prescription medicines or over-the-counter medicines such as vitamins, herbal products, or dietary supplements.

How often is INVEGA® SUSTENNA™ given?

INVEGA® SUSTENNA™ is a long-acting medicine that a healthcare professional will give you by injection. This means that you do not have to take this medicine every day.

When you receive your first dose of INVEGA® SUSTENNA™ you will need to get a second dose one week later. After that you will only need to get a dose once a month.

Your doctor or healthcare provider will give you the injection into the upper arm or buttocks. People usually feel some pain or discomfort. In clinical studies, most patients reported the injections became less painful over time.

What if I miss an injection of INVEGA® SUSTENNA™?

It is very important to keep all your appointments and get your injections on time. If you think you are going to miss your appointment, call your doctor or treatment team as soon as you can. Your doctor or treatment team will decide what you should do next.

What if I stop receiving INVEGA® SUSTENNA™?

If you stop coming for your injections, your symptoms may return. You should not stop receiving injections of this medicine unless you have discussed this with your doctor.

What are the possible side effects of INVEGA® SUSTENNA™?

As with any medicine, INVEGA® SUSTENNA™ may cause side effects in some people. If you think you are developing a side effect, always discuss this with your doctor or treatment team.

Common side effects of INVEGA® SUSTENNA™ include:

- Reactions at the injection site
- Sleepiness
- Dizziness
- Feeling of inner restlessness

- Abnormal muscle movements, including tremor (shaking), shuffling, uncontrolled involuntary movements, and abnormal movements of the eyes

Other important safety information

Neuroleptic Malignant Syndrome (NMS) is a rare, but serious side effect that could be fatal and has been reported with INVEGA® SUSTENNA™ and similar medicines. Call the doctor right away if you develop symptoms such as a high fever, rigid muscles, shaking, confusion, sweating more than usual, increased heart rate or blood pressure, or muscle pain or weakness. Treatment should be stopped if you are being treated for NMS.

Tardive Dyskinesia (TD) is a rare, but serious and sometimes permanent side effect reported with INVEGA® SUSTENNA™ and similar medicines. Call your doctor right away if you start to develop twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body. The risk of developing TD and the chance that it will become permanent is thought to increase with the length of therapy and the total dose received. This condition can also develop after a short period of treatment at low doses but this is less common. There is no known treatment for TD but it may go away partially or completely if the medicine is stopped.

One risk of INVEGA® SUSTENNA™ is that it may change your heart rhythm. This effect is potentially serious. You should talk to your doctor about any current or past heart problems. Because these problems could mean you're having a heart rhythm abnormality, contact your doctor **IMMEDIATELY** if you feel faint or feel a change in the way that your heart beats (palpitations).

High blood sugar and diabetes have been reported with INVEGA® SUSTENNA™ and similar medicines. If you already have diabetes or have risk factors such as being overweight or a family history of diabetes, blood sugar testing should be done at the beginning and during the treatment. The complications of diabetes can be serious and even life-threatening. Call your doctor if you develop signs of high blood sugar or diabetes, such as being thirsty all the time, having to urinate or "pass urine" more often than usual, or feeling weak or hungry.

Weight gain has been observed with INVEGA® SUSTENNA™ and other atypical antipsychotic medications. If you notice that you are gaining weight, please notify your doctor.

Some people may feel faint, dizzy, or may pass out when they stand up or sit up suddenly. Be careful not to get up too quickly. It may help if you get up slowly and sit

on the edge of the bed or chair for a few minutes before you stand up. These symptoms may decrease or go away after your body becomes used to the medicine.

INVEGA® SUSTENNA™ and similar medicines have been associated with decreases in the counts of white cells in circulating blood. If you have a history of low white blood cell counts or have unexplained fever or infection, then please contact your doctor right away.

INVEGA® SUSTENNA™ and similar medicines can raise the blood levels of a hormone called prolactin and blood levels of prolactin remain high with continued use. This may result in some side effects including missed menstrual periods, leakage of milk from the breasts, development of breasts in men, or problems with erection.

If you have a prolonged or painful erection lasting more than 4 hours, seek immediate medical help to avoid long-term injury.

Call your doctor right away if you start thinking about suicide or wanting to hurt yourself.

INVEGA® SUSTENNA™ can make some people feel dizzy, sleepy, or less alert. Until you know how you are going to respond to INVEGA® SUSTENNA™, be careful driving a car, operating machines, or doing things that require you to be alert.

This medicine may make you more sensitive to heat. You may have trouble cooling off or be more likely to become dehydrated. Be careful when you exercise or spend time doing things that make you warm.

Do not drink alcohol while you are taking INVEGA® SUSTENNA™.

This is not a complete list of all possible side effects. Ask your doctor or treatment team if you have any questions or want more information.

How can I get the most benefit from my INVEGA® SUSTENNA™ treatment?

- **Remember to keep all your appointments.** You need to receive your INVEGA® SUSTENNA™ treatments on time and your treatment team needs to check your progress. If you are going to miss an appointment, call your doctor's office right away so you can get your next dose as soon as possible.
- **Keep a list of questions.** Discuss this list with your treatment team at your next visit. Your treatment team wants to know how the medicine is working so they can give you the best care possible.
- **Be patient**. It may take some time before your symptoms of schizophrenia start to improve.
- **Follow the plan developed by you and your treatment team**. Remember that INVEGA® SUSTENNA™ is one part of your overall treatment plan.

Where can I find more information about INVEGA® SUSTENNA™?

This is a summary of important information about INVEGA® SUSTENNA™. If you have any questions about this information, talk with your doctor or treatment team.

You can also visit the website at www.invegasustenna.com or call the toll-free number at 1-800-JANSSEN (1-800-526-7736) for more information about INVEGA® SUSTENNA™.

Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Revised: July 2009

Exhibit 3

FDA Approval Letter for INVEGA SUSTENNA™(Paliperidone Palmitate) Extended-Release Injectable Suspension

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-264

NDA APPROVAL

Ortho-McNeil-Jansen Pharmaceuticals, Inc.
Attention: Rodney Malchow
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, N.J. 80560

Dear Mr. Malchow:

Please refer to your new drug application (NDA) dated October 25, 2007, received October 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega Sustenna (paliperidone palmitate) 39mg, 78mg, 117mg, 156mg, and 234 mg extended-release injectable suspension.

We acknowledge receipt of your submissions and communications dated February 2, 2009, February 11, 2009, February 24, 2009, March 24, 2009, May 7, 2009, May 15, 2009, May 20, 2009, May 22, 2009, June 9, 2009, June 22, 2009, June 26, 2009, July 10, 2009, July 15, 2009, July 16, 2009, July 20, 2009 and July 23, 2009.

Your February 2, 2009 submission constituted a complete response to our August 25, 2008 action letter.

This new drug application provides for the use of Invega Sustenna (paliperidone palmitate) extended-release injectable suspension for the acute and maintenance treatment of schizophrenia in adults.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm155657.htm. that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version

to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-264.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as agreed upon in your communication dated July 29, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-264.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Invega Sustenna, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 12 years because necessary studies are impossible or highly impracticable due to the very low incidence of schizophrenia diagnosed prior to age 13.

We are deferring submission of your pediatric studies for ages 13 to 17 years because pediatric studies in this age group should be delayed until additional safety and effectiveness data have been collected. Studies for the extended-release injectable suspension are deferred until studies currently being conducted under the adolescent schizophrenia development program are complete.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study to obtain pharmacokinetic data and provide information pertinent to

dosing of paliperidone palmitate extended-release injectable suspension in the relevant pediatric population. This study will be initiated after submission of the reports from the ongoing pediatric oral paliperidone studies to support use of paliperidone in adolescents aged 13 – 17.

Final Protocol Submission:	by June 1, 2011
Study Completion Date:	by November 1, 2013
Final Report Submission:	by January 1, 2014

2. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study of the efficacy and safety of paliperidone palmitate extended-release injectable suspension in the relevant pediatric population.

Final Protocol Submission:	by November 1, 2013
Study Completion Date:	by April 1, 2015
Final Report Submission:	by October 1, 2016

Submit clinical protocols to your IND for this product. Submit final reports to your NDA 22-264. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of the following postmarketing commitment agreed upon in our communication dated July 20, 2009.

3. You have committed to adding a clearly visible fill line to the syringe barrel so that the health care provider can ensure that the syringes contain the required volume of suspension prior to administration and that no gross leakage or evaporation of the syringe contents has occurred during storage or shipping. We request that this change be carried out, and a prior approval supplement be submitted within one year of approval.

Completion date: by August 2010

Under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to this postmarketing study commitment should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method and specifications for all strengths of the extended-release injectable suspension should be:

Parameter	**Dissolution Method and Specification**	
Apparatus Type	USP Type II (paddle)	
Media	0.001 M HCl containing 0.489% Polysorbate 20 (Tween®20)	
Volume	900 ml	
Temperature	25 ± 0.5 °C	
Frequency	50 rpm	
Sampling Times	1.5, 8, 20, and 45 minutes	
Acceptance Criteria	1.5 minutes	NMT 20% of Label Claim
	8 minutes	27% - 49% of Label Claim
	20 minutes	48% - 75% of Label Claim
	45 minutes	72% - 93% of Label Claim
Analysis	HPLC UV detection	

EXPIRY

A 24 month expiry date is granted based on the available stability data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and a copy to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (labeling)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN
07/31/2009

Exhibit 4

Copy of U.S. Patent No. 5,254,556

US005254556A

United States Patent [19]

Janssen et al.

[11] Patent Number: 5,254,556

[45] Date of Patent: * Oct. 19, 1993

[54] 3-PIPERIDINYL-1,2-BENZISOXAZOLES

[75] Inventors: Cornelus G. M. Janssen, Vosselaar; Alfonsus G. Knaeps, Herentals; Ludo E. J. Kennis, Turnhout; Jan Vandenberk, Beerse, all of Belgium

[73] Assignee: Janssen Pharmaceutica N.V., Beerse, Belgium

[*] Notice: The portion of the term of this patent subsequent to Oct. 27, 2009 has been disclaimed.

[21] Appl. No.: 932,142

[22] Filed: Aug. 19, 1992

Related U.S. Application Data

[60] Division of Ser. No. 422,847, Oct. 17, 1989, Pat. No. 5,158,952, which is a continuation-in-part of Ser. No. 267,857, Nov. 7, 1988, abandoned.

[51] Int. Cl.[5] C07D 487/04; C07D 413/04; A61K 31/505

[52] U.S. Cl. 514/258; 544/282

[58] Field of Search 544/282; 514/258

[56] References Cited

U.S. PATENT DOCUMENTS

4,804,663	2/1989	Kennis	544/282
5,151,424	9/1992	Janssens	544/282
5,158,952	10/1992	Janssen	544/282

Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Charles J. Metz

[57] ABSTRACT

The invention relates to C_{2-20}alkanoic acid esters of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6, 7,8,9-tetrahydro-9-hydroxy-2 -methyl-4H-pyrido[1,2-a]pyrimidin-4-one, pharmaceutically acceptable acid addition salts thereof, and enantiomeric forms thereof, which are useful in the treatment of warm-blooded animals suffering from psychotic diseases.

6 Claims, No Drawings

3-PIPERIDINYL-1,2-BENZISOXAZOLES

This application is a division of our copending application Ser. No. 422,847, filed Oct. 17, 1989, now U.S. Pat. No. [5,158,952], which in turn was a continuation-in-part of application Ser. No. 267,857, filed Nov. 7, 1988, now abandoned.

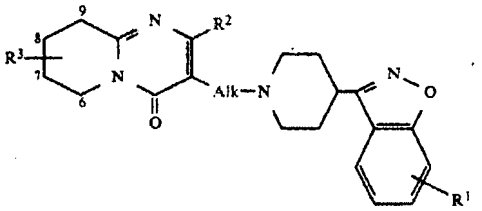
BACKGROUND OF THE INVENTION

In EP-A-0,196,132 there are described a number of 3-piperidinyl-1,2-benzisoxazoles having antipsychotic activity.

The compounds of the present invention differ therefrom by the specific substitution on the (2-C_{1-4}alkyl-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]-pyrimidin-3-yl)alkyl substituent at the 1 position of the piperidinyl moiety.

DESCRIPTION OF THE INVENTION

The present invention is concerned with novel 3-piperidinyl-1,2-benzisoxazoles having the formula



(I)

the pharmaceutically acceptable acid addition salts thereof, and the stereochemically isomeric forms thereof, wherein

Alk is C_{1-4}alkanediyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

R^2 is C_{1-4}alkyl;

R^3 is hydroxy or R^4—C(=O)O—; and

R_4 is C_{1-19}alkyl.

In the foregoing definitions C_{1-4}alkanediyl defines bivalent straight and branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the branched isomers thereof; C_{1-4}alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl; C_{1-19}alkyl defines C_{1-4}alkyl radicals as defined hereinabove and the higher homologs thereof having from 5 to 19 carbon atoms such as, for example, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and the like; halo is generic to fluoro, chloro, bromo and iodo. R^3 as defined hereinabove may be substituted on any of the 6,7,8 or 9 positions of the 6,7,8,9-tetrahydro-2-C_{1-4}alkyl-4H-pyrido[1,2-a]pyrimidin-4-one moiety.

Particular compounds are those compounds of formula (I) wherein R^3 is substituted on the 9 position of the 6,7,8,9-tetrahydro-2-C_{1-4}alkyl-4H-pyrido[1,2-a]pyrimidin-4-one moiety.

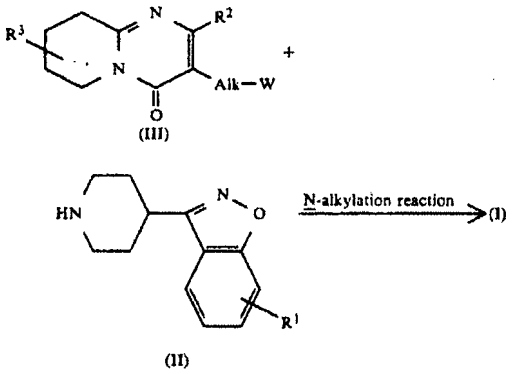
More particular compounds within the invention are those particular compounds wherein Alk is ethanediyl; and/or R^1 is halo, in particular fluoro and more in particular 6-fluoro; and/or R^2 is methyl.

Among the above defined groups of compounds of formula (I) those compounds wherein R^4 is C_{7-13}alkyl, in particular heptyl, nonyl, undecyl or tridecyl are of particular interest.

The most interesting compounds within the invention are selected from the group consisting of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, the pharmaceutically acceptable acid addition salt forms and the enantiomeric forms thereof.

From formula (I) it is evident that the compounds of this invention have at least one asymmetric carbon atom in their structure, namely the carbon atom bearing the R^3 substituent. The absolute configuration of this centre may be indicated by the stereochemical descriptors R and S, this R and S notation corresponding to the rules described in Pure Appl. Chem. 1976, 45, 11–30. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. Sterochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of the invention.

The compounds of formula (I) can generally be prepared by N-alkylating a 3-piperidinyl-1,2-benzisoxazole of formula (II) with an alkylating reagent of formula (III) following art-known N-alkylation procedures.



(III)

(II)

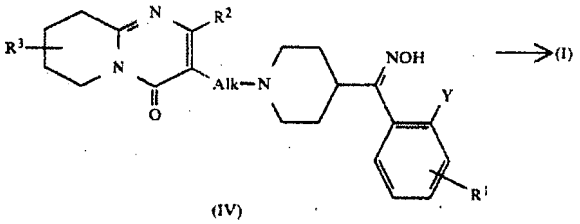
In formula (III) W represents an appropriate reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo; sulfonyloxy, e.g. methanesulfonyloxy, trifluoromethanesulfonyloxy, benzenesulfonyloxy, 4-methylbenzenesulfonyloxy and the like leaving groups. Said N-alkylation reaction can conveniently be carried out by mixing the reactants, optionally in a reaction-inert solvent such as, for example, water, an aromatic solvent, e.g. benzene, methylbenzene, dimethylbenzene, chlorobenzene, methoxybenzene and the like; a C_{1-6}alkanol, e.g. methanol, ethanol, 1-butanol and the like; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone and the like; an ester, e.g. ethyl acetate, γ-butyrolactone and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane and the like; a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, pyridine, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 1,3-dimethyl-2-imidazolidi-

none, 1,1,3,3-tetramethylurea, 1-methyl-2-pyrrolidinone, nitrobenzene, acetonitrile and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali metal or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, oxide, carboxylate, alkoxide, hydride or amide, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, calcium oxide, sodium acetate, sodium methoxide, sodium hydride, sodium amide and the like, or an organic base such as, for example, a tertiary amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, pyridine and the like, may optionally be used to pick up the acid which is formed during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, or a crown ether, e.g. 1,4,7,10,13,16-hexaoxa-cyclooctadecane and the like, may be appropriate. Stirring and somewhat elevated temperatures may enhance the rate of the reaction; more in particular the reaction may be conducted at the reflux temperature of the reaction mixture. Additionally, it may be advantageous to conduct said N-alkylation under an inert atmosphere such as, for example, oxygen-free argon or nitrogen gas.

Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions. Said conditions comprise stirring the reactants, with an appropriate base and optionally under an inert atmosphere as defined hereinabove, in the presence of a suitable phase transfer catalyst such as, for example, a trialkylphenylmethylammonium, tetraalkylammonium, tetraalkylphosphonium, tetraarylphosphonium halide, hydroxide, hydrogen sulfate and the like catalysts. Somewhat elevated temperatures may be appropriate to enhance the rate of the reaction.

In this and the following preparations, the reaction products may be isolated from the medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

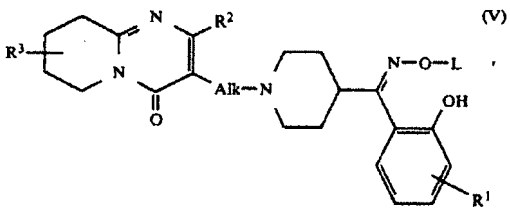
The compounds of formula (I) can also be obtained by the cyclization of an oxime of formula (IV), wherein Y is a reactive leaving group such as, for example, halo or nitro. Preferably Y is a halo group and more particularly fluoro.



(IV)

Said cyclization reaction of the oxime of formula (IV) may conveniently be conducted by treatment with an appropriate base, preferably in a suitable reaction-inert solvent at temperatures in the range of 20° to 200° C., preferably at 50° to 150° C., and in particular at the reflux temperature of the reaction mixture. Or, if desirable, said base may first be added, preferably at room temperature, whereupon the thus formed oxime salt is cyclized, preferably at an increased temperature and more preferably at the reflux temperature of the reaction mixture. Appropriate bases for said cyclization are, for example, alkali and earth alkaline metal carbonates, hydrogen carbonates, hydroxides, alkoxides or hydrides, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride or organic bases such as amines, e.g. N,N-diethylethanamine, 4-ethylmorpholine and the like bases. Suitable solvents are, for example, water; aromatic hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene and the like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane, 1,2-dichloroethane and the like; lower alkanols, e.g. methanol, ethanol, 1-butanol and the like; ketones, e.g. 2-propanone, 4-methyl-2-pentanone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like, or mixtures of such solvents.

The compounds of formula (I) can also be obtained by cyclizing an activated oxime derivative of formula



(V)

wherein L is an acid residue and more particularly is formyl, (C_{1-6}alkyl or aryl)-carbonyl, e.g. acetyl, propionyl, benzoyl and the like; (C_{1-6}alkyl or aryl)oxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, (1,1-dimethyl)ethoxycarbonyl, phenyloxycarbonyl and the like; (C_{1-6}alkyl or aryl)sulfonyl, e.g. methanesulfonyl, benzenesulfonyl, 4-methylbenzenesulfonyl, 2-naphthalenesulfonyl and the like; N-acylaminocarbonyl, e.g. trichloromethylcarbonylaminocarbonyl and the like. Said cyclization reaction of the activated oxime derivative of formula (V) may conveniently be conducted by treatment with an appropriate base, preferably in a suitable reaction-inert solvent, at temperatures in the range from 20° to 200° C., particularly from 50° to 150° C. and preferably at the reflux temperature of the reaction mixture. In some instances however, it may be advantageous not to add a base to the reaction mixture and to remove the acid liberated during the reaction by destillation at normal pressure or, if desired, at reduced pressure. Alternatively, said cyclization may also be effected by heating the oxime derivative (V) in vacuo without a solvent. Appropriate bases are for example, alkali and earth alkaline metal carbonates, hydrogen carbonates and organic amines, e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate, N,N-

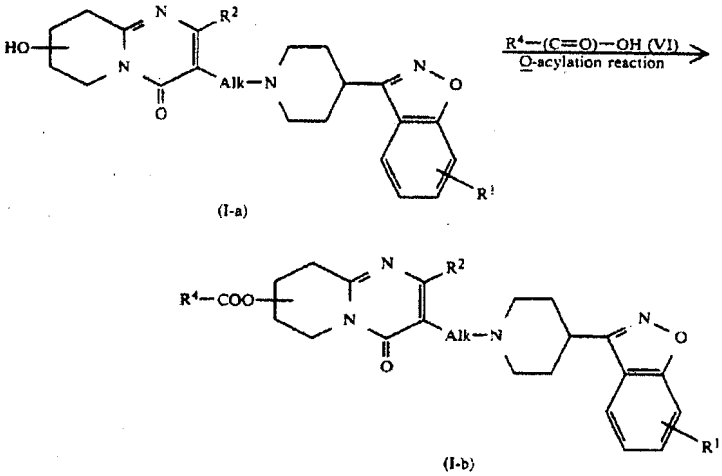
diethylethanamine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, pyridine and the like bases. Suitable solvents for said cyclization are, for example, aromatic hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene and the like; ethers, e.g. 1,1'-oxybisethane, 1,1'-oxybisbutane, tetrahydrofuran, 1,4-dioxane, 1,1'-oxybis[2-methoxyethane], 2,5,8,11-tetraoxadodecane and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, hexamethylphosphoric triamide, pyridine, acetic anhydride and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane, 1,2-dichloroethane, chlorobenzene and the like solvents.

The compounds of formula (I) wherein R^3 is R^4—(C=O)—O—, said compounds being represented by formula (I-b), can be obtained by the O-acylation reaction of a compound of formula (I-a) wherein R^3 is hydroxy, with a carboxylic acid of formula (VI) or a suitable reactive functional derivative thereof such as, for example, an acyl halide, symmetric or mixed anhydride, ester or amide, acyl azide and the like derivatives. Said functional derivatives may be prepared following art-known methods, for example, by reacting the carboxylic acid of formula (VI) with a halogenating reagent such as, for example, thionyl chloride, phosphorous trichloride, phosphoryl chloride, oxalyl chloride and the like, or by reacting said carboxylic acid (VI) with an acyl halide such as acetyl chloride and the like. Said derivatives may be generated in situ, or if desired, be isolated and further purified before reacting them with the compound of formula (I-a).

pyridinium iodide, phosphorus pentoxide, 1,1'-carbonylbis[1H-imidazole], 1,1'-sulfonyl bis[1H-imidazole] and the like reagents.

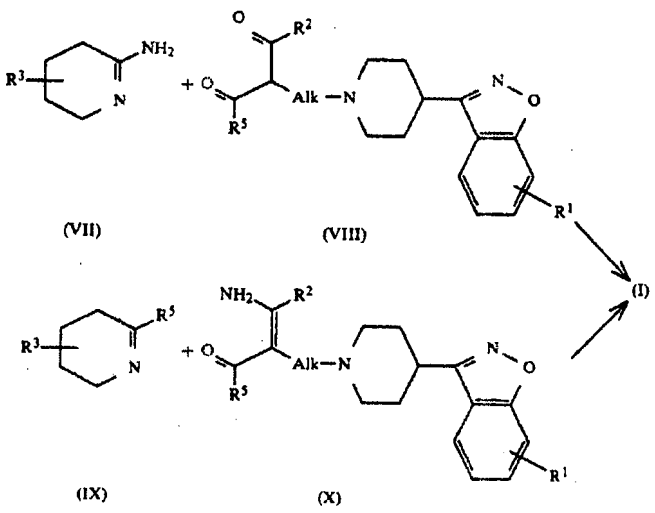
Said O-acylation reactions can conveniently be carried out by stirring the reactants optionally in a suitable reaction-inert solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane and the like; an aromatic hydrocarbon, e.g. benzene, methylbenzene and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran and the like; or a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, or pyridine and the like. In some instances it may be appropriate to employ an excess of one of the reagents as solvent. The water, acid, alcohol or amine which is liberated during the course of the reaction may be removed from the reaction mixture by art-known procedures such as, for example, azeotropical destillation, complexation, salt formation and the like methods. In some instances particularly the addition of a suitable base such as, for example, a tertiary amine, e.g. N,N-diethyl-ethanamine, 4-ethylmorpholine, pyridine or N,N-dimethyl-4-aminopyridine, may be appropriate. Further, in order to enhance the rate of the reaction, said acylation reaction may advantageously be conducted at a somewhat elevated temperature, and in particular instances at the reflux temperature of the reaction mixture.

The compounds of formula (I) can also be prepared following art-known cyclization procedures for preparing pyrimidin-4-ones such as, for example, by reacting an amidine of formula (VII) with a β-dicarbonyl intermediate of formula (VIII), or by cyclizing a reagent of



Alternatively, the compound of formula (I-a) and the carboxylic acid of formula (VI) may also be esterified in the presence of a suitable reagent capable of forming esters such as, for example, a dehydrating reagent, e.g. dicyclohexylcarbodiimide, 2-chloro-1-methyl-

formula (IX) with an enamine of formula (X). In formulae (VIII), (IX) and (X) R^5 represents an appropriate leaving group such as, for example, C_{1-6}alkyloxy, hydroxy, halo, amino, mono- or di-(C_{1-6}alkyl)amino and the like.



(VII) (VIII) (I)

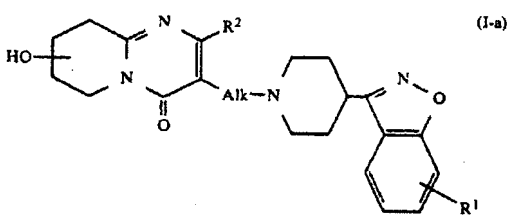
(IX) (X)

Said cyclization reactions may generally be carried out by stirring the reactants, optionally in the presence of a suitable reaction-inert solvent such as, for example, an aliphatic, alicyclic or aromatic hydrocarbon, e.g. hexane, cyclohexane, benzene and the like; pyridine, N,N-dimethylformamide and the like dipolar aprotic solvents. In order to enhance the rate of the reaction it may be appropriate to increase the temperature, more particularly, it may be recommendable to carry out the reaction at the reflux temperature of the reaction mixture.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic acid and the like, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted into the free base form by treatment with alkali.

The term acid addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) are able to form and said solvates are meant to be included within the scope of the present invention. Examples of such solvates are e.g., the hydrates, alcoholates and the like.

Enantiomeric forms of the compounds of formula (I-a)

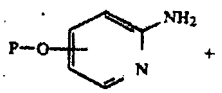


(I-a)

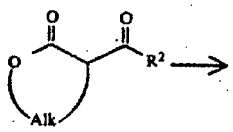
can be obtained by converting the racemic mixtures of the compounds of formula (I-a) with a suitable resolving reagent such as, for example, a chiral acid, e.g. tartaric, malic and mandelic acids, campher sulfonic acid, 4,5-dihydro-1H-2-benzopyran-2-carboxylic acid and the like, or the reactive functional derivatives thereof, e.g. the acyl halides, to a mixture of diastereomeric salts or compounds, particularly esters; physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomeric forms of the compounds of formula (I-a) by hydrolysis in an acidic or basic aqueous medium, optionally at an elevated temperature.

Some of the intermediates and starting materials for use in the foregoing preparations are known compounds, while others are novel. The intermediates of formula (II) and methods of preparing them are known from EP-A-0,196,132. The alkylating reagents of formula (III) are novel and can be prepared according to art-known methodologies of preparing similar compounds and will be described hereinafter in more detail.

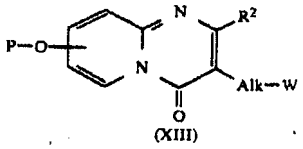
By condensing an optionally protected 2-aminopyridine derivative (XI) with an α-acyl lactone (XII) in the presence of an activating reagent in a suitable reaction-inert solvent, an intermediate of formula (XIII) can be obtained.



(XI)



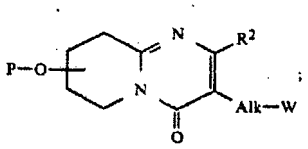
(XII)



(XIII)

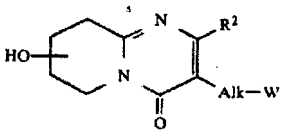
In the formulae (XI), (XIII) and hereinafter whenever it occurs, P represents hydrogen or a protective group which can be readily removed such as, for example, a hydrogenolyzable group, e.g. phenylmethyl and the like; a hydrolyzable group, e.g. methyl and the like. Appropriate activating reagents for said condensation reaction typically are halogenating reagents such as, for example, phosphoryl chloride, phosphoryl bromide, phosphorous trichloride, thionyl chloride and the like reagents.

The subsequent catalytic hydrogenation of intermediate (XIII) in a suitable reaction-inert solvent in the presence of hydrogen, optionally at an elevated temperature and/or pressure, with a catalyst such as, for example, palladium-on-charcoal and the like, can yield a protected intermediate (XIV) in case P is an alkyl group such as, for example, methyl;



(XIV)

or, on the other hand, when P is hydrogen or a hydrogenolyzable group such as, for example, phenylmethyl, an alkylating reagent of formula (III-a) wherein R^3 is hydroxy can be obtained directly.

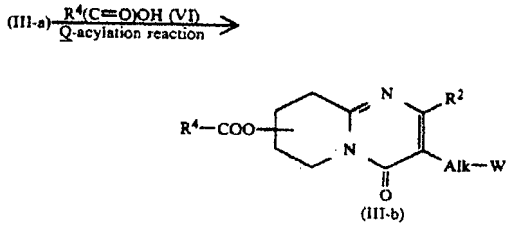


(II-a)

Suitable solvents for said catalytic hydrogenation reaction comprise water; C_{1-4}alkanols, e.g. methanol, ethanol, 2-propanol and the like; ethers, e.g. 1,1'-oxybisethane, 1,4-dioxane, tetrahydrofuran, 2-methoxyethanol and the like; halogenated hydrocarbons, e.g. trichloromethane and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide and the like; esters, e.g. ethyl acetate, butyl acetate and the like; or a mixture of such solvents.

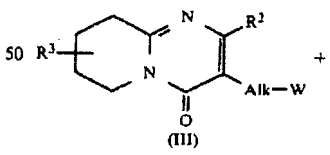
The intermediate (XIV) wherein P represents an alkyl group may be deprotected to a reagent of formula (III-a) by heating the former with concentrated hydrobromic or hydroiodic acid or by reaction with Lewis acids such as, for example, boron trihalides, e.g. boron trifluoride, boron trichloride and in particular boron tribromide; iodotrimethylsilane; or aluminum chloride and the like Lewis acids.

The intermediate of formula (III-a) may be O-acylated with a carboxylic acid of formula (VI) or a functional derivative thereof as defined hereinabove, to an alkylating reagent of formula (III-b) wherein R^3 is R^4—C(=O)—O— following the same procedures as described hereinabove for the O-acylation of the compounds of formula (I-a).

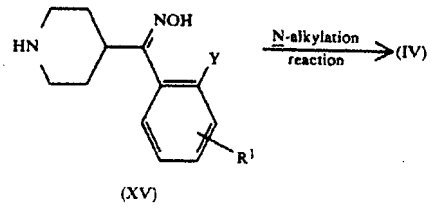


(III-b)

The intermediates of formula (IV) may be prepared by N-alkylating a reagent of formula (III) with an oxime derivative of formula (XV) following the same procedures as described hereinabove for the preparation of the compounds of formula (I) from the intermediates (II) and (III). The derivatives (XV) are known from EP-A-0,196,132.

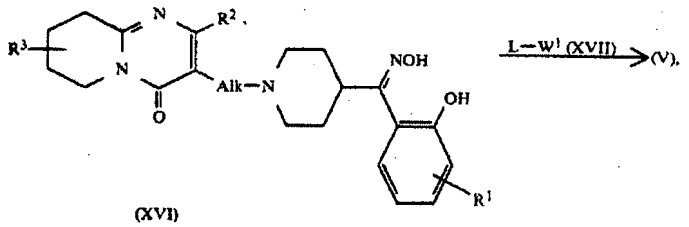


(III)



(XV)

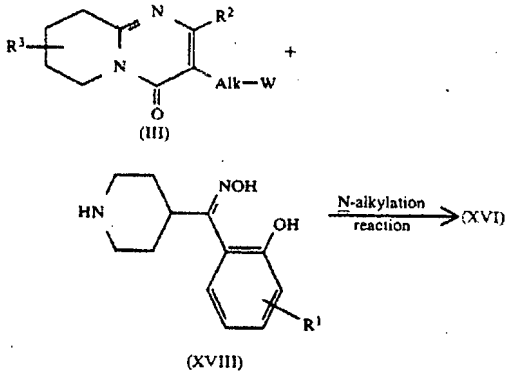
The intermediates of formula (V) may be obtained by reacting an oxime of formula (XVI) with an activated acid derivative of formula L-W^1 (XVII).



(XVI)

wherein L is an acid residue as defined hereinabove and W^1 represents a reactive leaving group such as, for example, halo, (aryl or C_{1-6}alkyl)carbonyloxy, (aryl or C_{1-6}alkyl)oxy and the like. As typical examples of the reagent of formula (XVII) there may be mentioned carboxylic acid anhydrides, e.g. acetic anhydride, benzoic anhydride and the like; carboxylic acid halides, e.g. acetyl chloride, benzoyl chloride and the like; carbonochloridates, e.g. methyl, ethyl or phenyl carbonochloridate and the like; di(C_{1-6}alkyl)carbonates, e.g. dimethylcarbonate, diethylcarbonate and the like. The reaction of the intermediates (XVI) with the activated acid derivatives (XVII) may be carried out following art-known esterification procedures, e.g. by stirring the reactants at a somewhat elevated temperature, preferably in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene and the like; a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane and the like; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g. 1,1'-oxybisethane, 1,4-dioxane and the like, a dipolar aprotic solvent, e.g. N,N-dimethylformamide, pyridine and the like solvents. In some instances it may be appropriate to add a suitable base such as, for example, N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, N,N-dimethyl-4-aminopyridine and the like bases to the reaction mixture.

The intermediate of formula (XVI) in turn may be prepared by N-alkylating a reagent of formula (III) with an oxime derivative of formula (XVIII)



following the same procedures as described hereinabove for the preparation of the compounds of formula (I) from the intermediates (II) and (III).

The compounds of formula (I) and some of the intermediates in the present invention contain at least one asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers.

Pure stereochemically isomeric forms of the compounds of formula (I) may also be obtained from the pure stereochemically forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stercochemically isomeric forms thereof, are potent antagonists of neurotransmitters and in particular of the mediators serotonin and dopamine. Antagonizing said mediators will suppress or relieve a variety of symptoms associated with phenomena induced by the release, in particular the excessive release, of these mediators. Therapeutic indications for using the present compounds are mainly in the CNS area, the gastrointestinal and cardiovascular field and related domains. The compounds of formula (I) are particularly useful as antipsychotic agents. Serotonin antagonists are reportedly effective in combatting psychoses, aggressive behaviour, anxiety, depression and migraine. Dopamine receptor antagonists are known to have neuroleptic properties. Combined serotonin-dopamine antagonists are especially interesting as they appear to offer relief of both the positive and negative symptoms of schizophrenia. Further the present compounds also appear to be useful therapeutic agents for combatting autism. Therapeutic applications in the gastrointestinal field comprise their use as, for instance, anti-diarrhoeals, inhibitors of gastro-oesophageal reflux and particularly antiemetics, e.g. in cancer patients receiving chemotherapy and radiation treatment. Further, serotonin is a potent broncho- and vasoconstrictor and thus the present antagonists may be used against hypertension and vascular disorders. In addition, serotonin antagonists have been associated with a number of other properties such as, the suppression of appetite and promotion of weight loss, which may prove effective in combating obesity; and also the

alleviation of withdrawal symptoms in addicts trying to discontinue drinking and smoking habits.

The compounds of formula (I) show the additional advantage of being eliminated rather slowly from the body and thus of being long acting. This can be evidenced, for example, by measuring the plasma levels after oral administration to dogs and by the long acting antiemetic effect exerted by the present compounds on dogs challenged with the dopamine agonist apomorphine. Especially the compounds of formula (I) wherein R^3 is a higher alkylcarbonyloxy radical have a long duration of action. Hence, the compounds of formula (I) only need to be administered at relatively large intervals, e.g. several days or weeks, the actual time of administration depending on the nature of the compound of formula (I) used and the condition of the subject to be treated. Consequently, the present compounds allow for a more efficient therapy: the slow elimination facilitates maintaining a stable plasma concentration at a non-toxic, effective level and the reduction in the number of administrations may be expected to result in better compliance of the subject to be treated with the prescribed medication.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in acid addition salt or base form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) wherein R^3 is R^4—C(=O)—O— may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage of unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In view of the usefulness of the subject compounds in the treatment of diseases associated with the release of neurotransmitters, in particular in the treatment of psychotic diseases, it is evident that the present invention provides a method of treating warm-blooded animals suffering from such diseases, in particular psychotic diseases, said method comprising the systemic administration of an antipsychotic amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, effective in treating diseases associated with the release of neurotransmitters, in particular psychotic diseases. Those of skill in the treatment of such diseases could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective antipsychotic amount would be from about 0.01 mg/kg to about 4 mg/kg body weight, more preferably from about 0.04 mg/kg to about 2 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

EXPERIMENTAL PART

A. Preparation of Intermediates

EXAMPLE 1

a) To a stirred mixture of 84 parts of phosphoryl chloride and 540 parts of methylbenzene were added 20 parts of 3-(phenylmethoxy)-2-pyridinamine. The mixture was stirred at 50° C. and 22 parts of 3-acetyl-4,5-dihydro-2(3H)-furanone were added. The reaction mixture was stirred for 5 hours at 90° C. Another portion of 22 parts of 3-acetyl-4,5-dihydro-2(3H)-furanone was added and stirring was continued for 30 minutes at 90° C. The solution was allowed to stand overnight at 90° C. The whole was poured into crushed ice and treated with an ammonium hydroxide solution 25%. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was stirred in 2-propanol. The product was filtered off, washed with a mixture of 2-propanol and 1,1'-oxybisethane and dried at 50° C., yielding 20.5 parts (62.3%) of 3-(2-chloroethyl)-2-methyl-9-(phenylmethoxy)-4H-

pyrido[1,2-a]pyrimidin-4-one; mp. 141.1° C. (intermediate 1)

b) A mixture of 3.3 parts of 3-(2-chloroethyl)-2-methyl-9-(phenylmethoxy)-4H-pyrido[1,2-a]pyrimidin-4-one and 120 parts of methanol was hydrogenated at normal pressure and at room temperature with 2.0 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated to dry, yielding 2.4 parts (99%) of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one as an oily residue. (intermediate 2)

EXAMPLE 2

a) A mixture of 17 parts of 5-methoxy-2-pyridinamine, 61 parts of phosphoryl chloride and 348 parts of methylbenzene was stirred for 2 hours at 60° C. 18 Parts of 3-acetyl-4,5-dihydro-2(3H)-furanone were added and the reaction mixture was stirred overnight at 90° C. The whole was poured into crushed ice and treated with ammonium hydroxide. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was stirred in a mixture of hexane and ethyl acetate (50:50 by volume). The precipitated product was filtered off and dried, yielding 10 parts (30.4%) of 3-(2-chloroethyl)-7-methoxy-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one; mp. 150° C. (intermediate 3)

b) A mixture of 10 parts of 3-(2-chloroethyl)-7-methoxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 40 parts of 2-propanol saturated with hydrogen chloride and 160 parts of methanol was hydrogenated at normal pressure and at room temperature with 2.0 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth and the filtrate was evaporated. The oily residue was taken up in 80 parts of 2-propanol and 2,2'-oxybispropane. After stirring overnight at room temperature, the precipitated product was filtered off, washed with a mixture of 2-propanol and 2,2'-oxybispropane and dried in vacuo at 50° C., yielding 7.5 parts (64.0%) of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-7-methoxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride; mp. 170° C. (intermediate 4)

c) A mixture of 6 parts of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-7-methoxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 4.8 parts of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole monohydrochloride, 6.1 parts of N-(1-methylethyl)--2-propanamine and 16 parts of methanol was stirred overnight at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 8.5 parts (100%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-7-methoxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one as an oily residue. (intermediate 5)

B. Final Compounds

EXAMPLE 3

A mixture of 12.5 parts of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one, 10.0 parts of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole monohydrochloride, 10 parts of N-(1-methylethyl)-2-propanamine and 120 parts of methanol was stirred overnight at 60° C. The reaction mixture was evaporated and the oily residue was taken up in trichloromethane and washed with water. The organic layer was dried, filtered and evaporated. The residue was purified twice by column chromatography over silica gel first using a mixture of trichloromethane and methanol (95:5 by volume) and then a mixture of trichloromethane and methanol, saturated with ammonia (95:5 by volume) as eluents. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanone. After cooling, the precipitated product was filtered off, washed with a mixture of 2-propanol and 2,2'-oxybispropane and recrystallized from 2-propanol. The product was filtered off and dried, yielding 3.6 parts (21.1%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 179.8° C. (Compound 1)

EXAMPLE 4

To a stirred solution of 5.4 parts of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one and 1.6 parts of N,N-dimethyl-4-pyridinamine in 39 parts of dichloromethane was added dropwise a solution of 5.4 parts of (+)-3,4-dihydro-1H-2-benzopyran-2-carbonyl chloride in 39 parts of dichloromethane. Upon complete addition, stirring was continued for 4 hours at room temperature. The reaction mixture was washed successively with water, a sodium hydroxide solution 1N and water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of acetonitrile and water, saturated with ammonia (50:50 by volume) as eluent. Two pure fractions were collected and the eluent was evaporated. Each residue was salted out with sodium chloride and two diastereo-isomeric esters were obtained. The first isomer was combined with 16 parts of methanol, 1 parts of N-(1-methyl-ethyl)-2-propanamine and 1 part of water and the whole was stirred for 160 minutes at 60° C. The mixture was evaporated and the residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 0.2 parts (3.6%) of (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one; mp. 160.7° C., $[\alpha]^{D} = +15.42°$ (c=0.5% in ethanol). (Compound 2)

The second isomer was combined with 16 parts of methanol, 1 part of N-(1-methylethyl)-2-propanamine and 1 part of water and the whole was stirred for 160 minutes at 60° C. The mixture was evaporated and the residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 0.2 parts (3.6%) of (−)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one; mp. 156.9° C., $[\alpha]^{D} = -22.81°$ C. (c=0.5% in ethanol). (Compound 3)

EXAMPLE 5

A mixture of 4.3 parts of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and 30 parts of acetic acid anhydride was stirred for 4 hours at 50° C. After cooling, the reaction mixture was poured into water and treated with an ammonium hydroxide solution. The product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated in vacuo. The residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 3.0 parts (64.0%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-acetate(ester); mp. 143.6° C. (Compound 4) In a similar manner and by using butanoic acid anhydride as acylating reagent there was also prepared [3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl]butanoate, mp. 112.9° C. (Compound 5).

EXAMPLE 6

To a stirred solution of 1.2 parts of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one in 21 parts of dichloromethane and 5 parts of water were simultaneously added dropwise a solution of 1.1 parts of decanoyl chloride in 13 parts of dichloromethane and a solution of 1 part of sodium hydroxide in 6 parts of water. Upon complete addition, stirring was continued for 2 hours at room temperature. Another portion of 1.1 parts of decanoyl chloride was added and stirring was continued overnight at room temperature. The product was extracted with dichloromethane. The extract was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in 2-propanol. The product was filtered off and dried, yielding 0.9 parts (45.9%) of [3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl]decanoate dihydrochloride; mp. 221.4° C. (Compound 6)

EXAMPLE 7

A mixture of 8.5 parts of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-7-methoxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 14 parts of iodotrimethylsilane and 40 parts of acetonitrile was stirred overnight at 70° C. Another portion of 2,8 parts of iodotrimethylsilane was added and the reaction mixture was stirred for a while at 90° C. and then overnight at reflux temperature. After cooling, the whole was evaporated. The residue was taken up in ethanol and the whole was evaporated again. The residue was taken up in water and treated with a sodium hydroxide solution. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was solidified in ethanol. The product was filtered off and dried, yielding 0.3 parts (3.7%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-7-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one; mp. 156.2° C. (Compound 7)

Following the procedure of example 6, compound 7 was converted to [3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]-pyrimidin-7-yl]decanoate. (Compound 8)

C. Pharmacological Examples

EXAMPLE 8

The antipsychotic activity of the subject compounds is evidenced by the experimental data obtained in at least one of two different test procedures, viz. the combined apomorphine (APO), tryptamine (TRY) and norepinephrine (NOR) test in rats, and the apomorphine test in dogs. Said combined apomorphine, tryptamine and norepinephrine test is described in Ach. int. Pharmacodyn., 227, 238–253 (1977) and provides an empirical evaluation of the relative specificity with which drugs may effect particular neurotransmitter systems centrally (CNS) as well as peripherally. In particular, the test demonstrates the antagonistic activity of the tested compounds of formula (I) on dopamine (by preventing the symptoms elicited with the dopamine agonist apomorphine), on serotonin (by preventing the central and peripheral symptoms (convulsions; hyperaemia) elicited with serotonin or tryptamine), and on norepinephrine (by preventing or delaying death upon administration of the α_2-agonist norepinephrine). Said apomorphine test in dogs is described in Arzneim.-Forsch. (Drug Res.), 9, 765–767 (1959) and provides a measure of the duration of action of the tested compounds. The tests are carried out following the procedures described in EP-A-0,196,132 and the experimental data are summarized in Table 1.

TABLE 1

Comp No.	Combined test in rats; ED_{50} in mg/kg (APO)	(TRY)-convulsions	(TRY)-hyperaemia	(NOR)	(APO)-dog test, ED_{50} in mg/kg 1 hr	4 hr	16 hr
1	0.25	0.31	0.002	0.08	0.015	0.015	0.015
2	0.31	0.08	0.00031	1.25	0.015	0.03	0.06
3	0.31	0.31	0.00063	0.63	0.008	0.007	0.015
4	0.31	0.08	0.00031	0.31	0.015	*	*
5	0.31	0.31	0.00125	0.16	0.008	*	*

*not tested.

D. Composition Examples

EXAMPLE 9

Oral Drops

500 Parts of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5l of the polyethylene glycol at 60° ~ 80° C. After cooling to 30° ~ 40° C. there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 parts of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I..

The resulting solution was filled into suitable containers.

EXAMPLE 10

Oral Solution

9 Parts of methyl 4-hydroxybenzoate and 1 part of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 31 l of this solution were dissolved first 10 parts of 2,3-dihydroxybutanedioic acid and thereafter 20 parts of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Parts of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

EXAMPLE 11

Capsules

20 Parts of the A.I., 6 parts sodium lauryl sulfate, 56 parts starch, 56 parts lactose, 0.8 parts colloidal silicon dioxide, and 1.2 parts magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, comprising each 20 mg of the active ingredient.

EXAMPLE 12

Film-Coated Tablets

Preparation of tablet core

A mixture of 100 parts of the A.I., 570 parts lactose and 200 parts starch was mixed well and thereafter humidified with a solution of 5 parts sodium dodecyl sulfate and 10 parts polyvinylpyrrolidone (Kollidon-K 90 ®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 parts microcrystalline cellulose (Avicel ®) and 15 parts hydrogenated vegetable oil (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 parts methyl cellulose (Methocel 60 HG ®) in 75 ml of denaturated ethanol there was added a solution of 5 parts of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Parts of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 parts of magnesium octadecanoate, 5 parts of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109 ®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

EXAMPLE 13

Injectable Solution

1.8 Parts methyl 4-hydroxybenzoate and 0.2 parts propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50° C. there were added while stirring 4 parts lactic acid, 0.05 parts propylene glycol and 4 parts of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

EXAMPLE 14

Suppositories

3 Parts A.I. was dissolved in a solution of 3 parts 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Parts surfactant (SPAN ®) and triglycerides (Witepsol 555 ®) q.s. ad 300 parts were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37°-38° C. to form 100 suppositories each containing 30 mg/ml of the A.I.

EXAMPLE 15

Injectable Solution

60 Parts of A.I. and 12 parts of benzylalcohol were mixed well and sesame oil was added q.s. ad 1 l, giving a solution comprising 60 mg/ml of A.I. The solution was sterilized and filled in sterile containers.

We claim:

1. A compound selected from the group consisting of a C_{2-20}alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, a pharmaceutically acceptable acid addition salt thereof, and an enantiomeric form thereof.

2. An antipsychotic composition comprising an inert carrier and as active ingredient an antipsychotic effective amount of the compound of claim 1.

3. A method of treating warm-blooded animals suffering from psychotic diseases, which method comprises the administration to said warm-blooded animals of an antipsychotic effective amount of the compound of claim 1.

4. The compound of claim 1 wherein the alkanoic acid is octanoic acid, decanoic acid, dodecanoic acid, or tetradecanoic acid.

5. The composition of claim 2 wherein the alkanoic acid is octanoic acid, decanoic acid, dodecanoic acid, or tetradecanoic acid.

6. The method of claim 3 wherein the alkanoic acid is octanoic acid, decanoic acid, dodecanoic acid, or tetradecanoic acid.

* * * * *

Exhibit 5

Copy of U.S. Patent & Trademark Office Maintenance Fee Statement for U.S. Patent No. 5,254,556

United States Patent and Trademark Office

Patent Bibliographic Data					06/24/2009 12:37 PM
Patent Number:	5254556		**Application Number:**	07932142	
Issue Date:	10/19/1993		**Filing Date:**	08/19/1992	
Title:	NOVEL 3-PIPERIDINYL-1,2-BENZISOXAZOLES				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	03/29/2005 03/16/2001 03/25/1997	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	AUDLEY A. CIAMPORCERO JOHNSON AND JOHNSON ONE JOHNSON AND JOHNSON PLAZA NEW BRUNSWICK, NJ 089337003				

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NEW BRUNSWICK NJ 08933-7003

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,254,556	**$1,020.00**	**$0.00**	**03/25/97**	**07/932,142**	**10/19/93**	**08/19/92**	**04**	**NO**	**JAB-828**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,254,556	**$1,950.00**	**$0.00**	**03/16/01**	**07/932,142**	**10/19/93**	**08/19/92**	**08**	**NO**	**JAB-828**

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,254,556	**$3,800.00**	**$0.00**	**03/29/05**	**07/932,142**	**10/19/93**	**08/19/92**	**12**	**NO**	**JAB-828**

Exhibit 6 **Terminal Disclaimer**

JAB 828

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Cornelius G. M. Janssen et al.		
Serial No.	:	07/932,142	Art Unit:	1202
Filed	:	August 19, 1992	Examiner:	J. Venkat
For	:	NOVEL 3-PIPERIDINYL-1,2-BENZISOXAZOLES		

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

TERMINAL DISCLAIMER

Your Petitioner, JANSSEN PHARMACEUTICA N.V., a corporation of Belgium, having an address at Turnhoutseweg 30, B-2340 Beerse, Belgium, represents that it is the Assignee of the entire right, title and interest in and to the subject matter disclosed in the above-captioned patent application by virtue of its being a divisional of U.S. Patent Application Serial No. 07/422,847, filed October 17, 1989, which was assigned to JANSSEN PHARMACEUTICA N.V., the assignment being recorded in the United States Patent and Trademark Office on November 13, 1989, on Reel 5171, Frame 0567.

Your Petitioner, JANSSEN PHARMACEUTICA N.V., hereby disclaims, under the provisions of 35 U.S.C. 253, the terminal part of any patent granted on application Serial No. 07/932,142 which would extend beyond the expiration date of United States Patent No. 5,158,952, also assigned to JANSSEN PHARMACEUTICA N.V. (recorded on November 13, 1989, on Reel 5171, Frame 0567), and hereby agrees that any patent so granted on application Serial No. 07/932,142 shall be enforceable only for and during such period that the legal title of said patent shall be the same as the legal title to United States Patent No. 5,158,952, this agreement to run with any patent granted on application Serial No. 07/932,142 and to be binding upon the grantee, its successors or assigns.

Signed at Beerse (Belgium) this 7th day of December, 1992.

Respectfully submitted,

JANSSEN PHARMACEUTICA N.V.

By: Wantet December 7, 1992

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Exhibit 7

Claims 1, 2 and 3 of U.S. Patent No. 5,254,556 Reads on the Ingredient of the Approved Product

1. A compound selected from the group consisting of a C_{2-20}alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, a pharmaceutically acceptable acid addition salt thereof, and an enantiomeric form thereof.	Paliperidone palmitate is a C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.
2. An antipsychotic composition comprising an inert carrier and as active ingredient an antipsychotic effective amount of the compound of claim 1.	The approved Product comprises paliperidone palmitate, a C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, and one or more inert carriers provided in an amount sufficient to treat schizophrenia (a psychotic disorder).
3. A method of treating warm-blooded animals suffering from psychotic diseases, which method comprises the administration to said warm-blooded animals of an antipsychotic effective amount of the compound of claim 1.	The approved Product is for the treatment of schizophrenia (a psychotic disease). The treatment comprises administering an antipsychotic effective amount of paliperidone palmitate, a C_{16} alkanoic acid ester of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Exhibit 8

DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
5/6/2003	Original IND	na	Original IND (50 Volumes)	na	000	Multiple	Original IND	na
5/13/2007	Record of Contact	5/13/2003	Request for Additional Desk Copies and IND Number for Paliperidone palmitate	na	na	2651976	EDMS-PSDB-2651976	na
5/19/2003	Record of Contact	5/19/2003	Request for List of Nonclinical Studies Submitted Under IND 67,356	na	na	2656702	EDMS-PSDB-2656702	na
5/28/2003	General Correspondence	na	Response to Request by Review Chemist	na	001	2676686	EDMS-PSDB-2676686	na
5/30/2003	General Correspondence	na	Response to Request from Dr. Lois Freed	na	002	2683477	EDMS-PSDB-2683477	na
6/2/2003	Record of Contact	6/2/2003	Clearance to Proceed with the Studies Under IND	na	na	2697285	EDMS-PSDB-2697285	na
6/5/2003	General Correspondence	na	Response to Request by Review Chemist	na	003	2716903	EDMS-PSDB-2716903	na
9/11/2003	Protocol Amendment	na	New Investigators	R092670-USA-3	004	2931978	EDMS-PSDB-2931978	na
9/12/2003	Information Amendment	na	CMC; Pharmacology/Toxicology	na	005	2937288	EDMS-PSDB-2937288	na
10/28/2003	Protocol Amendment	na	New Protocol; New Investigator	R092670-SCH-201	006	3044512	EDMS-PSDB-3044512	na
1/9/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	007	3195694	EDMS-PSDB-3195694	na
1/23/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	008	3230681	EDMS-PSDB-3230681	na
2/11/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	009	3288697	EDMS-PSDB-3288697	na
3/31/2004	Safety Report	na	US-JNJFOC-20040304794 Initial	R076477-SCH-304	010	3397560	EDMS-PSDB-3397560	na
4/22/2004	General Correspondence	na	Request for Type B End of Phase 2 Meeting - Chemistry, Microbiology, and Biopharmaceutics	na	011	3442328	EDMS-PSDB-3442328	na
4/29/2004	FDA Correspondence	na	Letter: Meeting Request Granted for 6/16/04	na	na	3548304	EDMS-PSDB-3548304	na
5/6/2004	General Correspondence	na	Request for a Type B End-of-Phase 2 Meeting	na	012	3474299	EDMS-PSDB-3474299	na
5/10/2004	Safety Report	na	US-JNJFOC-20040304794 F-1	R076477-SCH-304	013	3479851	EDMS-PSDB-3479851	na
5/20/2004	General Correspondence	na	Briefing Package for 6/16/04 CMC/Biopharm Meeting	na	014	3514273	EDMS-PSDB-3514273	na
6/16/2004	Record of Contact	6/16/2004	Minutes of 6/16/04 CMC/Biopharmaceutics End of Phase 2 Meeting for Paliperidone palmitate	na	na	3594054	EDMS-PSDB-3594054	na
6/28/2004	General Correspondence	na	Minutes of 6/16/04 Type B End of Phase 2 Meeting - CMC/Biopharmceutics		015	3599384	EDMS-PSDB-3599384	na
7/1/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	016	3609437	EDMS-PSDB-3609437	na
8/4/2004	Annual Report	na	Reporting Period: 6/7/03 - 6/6/04	na	017	3681428	EDMS-PSDB-3681428	na
8/12/2004	Safety Report	na	IN-JNJFOC-20040800656 Initial	R076477-SCH-303	018	3699361	EDMS-PSDB-3699361	na
8/17/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	019	3704542	EDMS-PSDB-3704542	na
8/25/2004	Safety Report	na	IN-JNJFOC-20040800656 F-1	R076477-SCH-303	020	3723435	EDMS-PSDB-3723435	na
8/27/2004	General Correspondence	na	Notice of Intent to Request Special Protocol Assessment: Carcinogenicity	na	021	3728621	EDMS-PSDB-3728621	na
8/27/2004	FDA Correspondence	na	Fax: Notice of Intent to Request Special Protocol Assessment: Carcinogenicity SN 021	na	na	3732055	EDMS-PSDB-3732055	na
9/2/2004	FDA Correspondence	na	Letter: IND Acknowledgement Letter	na	na	3776556	EDMS-PSDB-3776556	na
9/9/2004	IND Amendment	na	Briefing Package for 9/28/04 End of Phase 2 Meeting	na	022	3756672	EDMS-PSDB-3756672	na
10/1/2004	IND Amendment	na	Request for Special Protocol Assessment: Carcnogenicity Protocol	na	023	3810109	EDMS-PSDB-3810109	na
10/26/2004	IND Amendment	na	Follow-up Information for Request for Special Protocol Assessment: Carcinogenicity Protocol	na	024	3860095	EDMS-PSDB-3860095	na
10/26/2004	Record of Contact	9/28/2004	Minutes of the 9/28/04 End of Phase 2 FDA Meeting	na	na	3818660	EDMS-PSDB-3818660	na
10/26/2004	FDA Correspondence	na	Fax: 10/26/04 Submission SN 024	na	na	3928067	EDMS-PSDB-3928067	na
10/27/2004	General Correspondence	na	Minutes of the 9/28/04 End of Phase 2 Meeting and Post-Meeting Follow-up Information	na	025	3862824	EDMS-PSDB-3862824	na
10/28/2004	General Correspondence	na	Response to FDA Request in 10/12/04 End of Phase 2 CMC/Biopharm Meeting Minutes	na	026	3868773	EDMS-PSDB-3868773	na
11/9/2004	Protocol Amendment	na	New Protocol; New Investigator	R076477-PSY-3004	027	3902895	EDMS-PSDB-3902895	na
11/10/2004	General Correspondence	na	Request for a Type C Meeting	na	028	3907677	EDMS-PSDB-3907677	na
11/11/2004	Safety Report	na	US-JNJFOC-20041100394 Initial	R092670-SCH-704	029	3909784	EDMS-PSDB-3909784	na
11/15/2004	FDA Correspondence	na	Fax: Response to Carcinogenicity Protocol Assessment Request - Final CAC Report	na	na	3928113	EDMS-PSDB-3928113	na

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Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
11/18/2004	Information Amendment	na	CMC	na	030	3928878	EDMS-PSDB-3928878	na
11/22/2004	Safety Report	na	US-JNJFOC-20041102371 Initial	R076477-SCH-304	031	3931421	EDMS-PSDB-3931421	na
11/23/2004	Safety Report	na	US-JNJFOC-20041103584 Initial	R076477-SCH-304	032	3938295	EDMS-PSDB-3938295	na
11/23/2004	FDA Correspondence	na	Fax: Safety report SN 032	R076477-SCH-304	na	3961743	EDMS-PSDB-3961743	na
11/30/2004	Safety Report	na	US-JNJFOC-20041102371 F-1	R076477-SCH-304	033	3949874	EDMS-PSDB-3949874	na
11/30/2004	Information Amendment	na	Pharmacology/Toxicology; Clinical	na	034	3955196	EDMS-PSDB-3955196	na
12/2/2004	Safety Report	na	US-JNJFOC-20041103584 F-1	R076477-SCH-304	035	3961376	EDMS-PSDB-3961376	na
12/3/2004	Safety Report	na	MY-JNJFOC-20041105754 Initial	R076477-SCH-705	036	3963269	EDMS-PSDB-3963269	na
12/7/2004	Information Amendment	na	Pharmacology/Toxicology	na	037	3967273	EDMS-PSDB-3967273	na
12/10/2004	Safety Report	na	US-JNJFOC-20041201617 Initial	R076477-SCH-701	038	3976131	EDMS-PSDB-3976131	na
12/20/2004	Safety Report	na	IN-JNJFOC-20041202092 Initial	R076477-SCH-703	039	3998127	EDMS-PSDB-3998127	na
12/20/2004	General Correspondence	na	Briefing Package for 1/13/05 Meeting	na	040	3998804	EDMS-PSDB-3998804	na
12/23/2004	Safety Report	na	CA-JNJFOC-20041204345 Initial	R076477-SCH-305	041	4008929	EDMS-PSDB-4008929	na
12/23/2004	Safety Report	na	MY-JNJFOC-20041105754 F-1	R076477-SCH-705	042	4007899	EDMS-PSDB-4007899	na
12/27/2004	Safety Report	na	MY-JNJFOC-20041204460 Initial	R076477-SCH-705	043	4010952	EDMS-PSDB-4010952	na
12/27/2004	Safety Report	na	IN-JNJFOC-20041202092 F-1	R076477-SCH-703	044	4010959	EDMS-PSDB-4010959	na
12/27/2004	Safety Report	na	MY-JNJFOC-20041105754 F-2	R076477-SCH-705	045	4010966	EDMS-PSDB-4010966	na
1/4/2005	Safety Report	na	CA-NJFOC-20041204345 F-1	R076477-SCH-305	046	4019867	EDMS-PSDB-4019867	na
1/6/2005	Protocol Amendment	na	New Protocol; New Investigator	R092670-PSY-3001	047	4023920	EDMS-PSDB-4023920	na
1/7/2005	Safety Report	na	MY-JNJFOC-20041105754 F-3	R076477-SCH-705	048	4026257	EDMS-PSDB-4026257	na
1/14/2005	Safety Report	na	US-JNJFOC-20041100394 F-1	R076477-SCH-704	049	4042911	EDMS-PSDB-4042911	na
1/18/2005	Information Amendment	na	Pharmacology/Toxicology	na	050	4050521	EDMS-PSDB-4050521	na
1/18/2005	Safety Report	na	PL-JNJFOC-20041206244 Initial	R076477-SCH-703	051	4050379	EDMS-PSDB-4050379	na
1/19/2005	Safety Report	na	US-JNJFOC-20050103392 Initial	R076477-SCH-701	052	4056138	EDMS-PSDB-4056138	na
1/19/2005	FDA Correspondence	na	Fax: Safety Report SN 052	R076477-SCH-701	na	4063491	EDMS-PSDB-4063491	na
1/21/2005	Safety Report	na	US-JNJFOC-20050103392 F-1	R076477-SCH-701	053	4063195	EDMS-PSDB-4063195	na
1/24/2005	Safety Report	na	CA-JNJFOC-20041204345 F-2	R076477-SCH-305	054	4066354	EDMS-PSDB-4066354	na
1/26/2005	Safety Report	na	US-JNJFOC-20050103392 F-2	R076477-SCH-301	055	4070650	EDMS-PSDB-4070650	na
2/2/2005	Safety Report	na	US-JNJFOC-20050105338 Initial	R076477-SCH-305	056	4092677	EDMS-PSDB-4092677	na
2/2/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3004	057	4093088	EDMS-PSDB-4093088	na
2/3/2005	Safety Report	na	IN-JNJFOC-20041202092 F-2	R076477-SCH-703	058	4094614	EDMS-PSDB-4094614	na
2/4/2005	Safety Report	na	US-JNJFOC-20041100394 F-2	R076477-SCH-704	059	4098820	EDMS-PSDB-4098820	na
2/4/2005	Safety Report	na	MY-JNJFOC-20050105402 Initial	R076477-SCH-305	060	4098827	EDMS-PSDB-4098827	na
2/11/2005	Safety Report	na	RO-JNJFOC-20050201375 Initial	R076477-SCH-301	061	4115429	EDMS-PSDB-4115429	na
2/11/2005	FDA Correspondence	na	Fax: Safety Report SN 061	R076477-SCH-301	na	4140901	EDMS-PSDB-4140901	na
2/14/2005	Safety Report	na	US-JNJFOC-20050105338 F-1	R076477-SCH-305	062	4119644	EDMS-PSDB-4119644	na
2/17/2005	Safety Report	na	MY-JNJF)C-20050105402 F-1	R076477-SCH-305	063	4128519	EDMS-PSDB-4128519	na
2/22/2005	Safety Report	na	RO-JNJFOC-20050201375 F-1	R076477-SCH-301	064	4137747	EDMS-PSDB-4137747	na
3/23/2005	Safety Report	na	US-JNJFOC-20050304957 Initial	R076477-SCH-1009	065	4209442	EDMS-PSDB-4209442	na
3/23/2005	General Correspondence	na	Fax: Safety Report SN 065	R076477-SCH-1009	na	4210799	EDMS-PSDB-4210799	na
3/31/2005	Safety Report	na	US-JNJFOC-20050304957 F-1	R076477-SCH-1009	066	4224908	EDMS-PSDB-4224908	na
4/4/2005	Safety Report	na	TW-JNJFOC-20050305349 Initial	R076477-SCH-305	067	4233955	EDMS-PSDB-4233955	na
4/13/2005	Safety Report	na	MY-JNJFOC-20041204460 F-1	R076477-SCH-705	068	4255811	EDMS-PSDB-4255811	na
4/15/2005	Safety Report	na	MY-JNJFOC-20041204460 F-2	R076477-SCH-705	069	4259582	EDMS-PSDB-4259582	na
4/15/2005	Safety Report	na	NL-JNJFOC-20050402753 Initial	PALIOROS-SCH-1011	070	4267510	EDMS-PSDB-4267510	na
4/15/2005	General Correspondence	na	Fax: Safety Report SN 070	PALIOROS-SCH-1011	na	4278984	EDMS-PSDB-4278984	na
4/20/2005	Safety Report	na	US-JNJFOC-20050105338 F-2	R076477-SCH-305	071	4279747	EDMS-PSDB-4279747	na
4/20/2005	Safety Report	na	MY-JNJFOC-20041105754 F-4	R076477-SCH-705	072	4279761	EDMS-PSDB-4279761	na
4/20/2005	Safety Report	na	US-JNJFOC-20041100394 F-3	R076477-SCH-704	073	4279122	EDMS-PSDB-4279122	na
4/22/2005	Safety Report	na	NL-JNJFOC-20050402753 F-1	PALIOROS-SCH-1011	074	4287661	EDMS-PSDB-4287661	na
5/9/2005	IND Amendment	na	Reclassification of IND Safety Reports	na	075	4322913	EDMS-PSDB-4322913	na
5/9/2005	Protocol Amendment	na	New Protocol; New Investigator	R092670-PSY-3003	076	4322769	EDMS-PSDB-4322769	na

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Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
5/10/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3004	077	4325611	EDMS-PSDB-4325611	na
5/11/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3001	078	4329282	EDMS-PSDB-4329282	na
5/16/2005	Safety Report	na	US-JNJFOC-20050502821 Initial	R076477-SCH-1009	079	4343153	EDMS-PSDB-4343153	na
5/16/2005	FDA Correspondence	na	Fax: Safety Report SN 079	R076477-SCH-1009	na	4348879	EDMS-PSDB-4348879	na
5/23/2005	Safety Report	na	MY-JNJFOC-20041204460 F-3	R076477-SCH-705	080	4354981	EDMS-PSDB-4354981	na
5/25/2005	Safety Report	na	IN-JNJFOC-20050503897 Initial	R076477-SCH-301	081	4362170	EDMS-PSDB-4362170	na
5/25/2005	Safety Report	na	IN-JNJFOC-20050503897 F-1	R076477-SCH-301	082	4381574	EDMS-PSDB-4381574	na
6/10/2005	Information Amendment	na	CM&C	R092670-PSY-3003	083	4403047	EDMS-PSDB-1103047	na
6/13/2005	General Correspondence	na	Request for Review of Drug Product Registration Stability Protocol	na	084	4411495	EDMS-PSDB-4411495	na
6/14/2005	Information Amendment	na	Change in Protocol	R092670-PSY-3001	085	4411736	EDMS-PSDB-4411736	na
6/14/2005	Information Amendment	na	Change in Protocol	R092670-PSY-3004	086	4411745	EDMS-PSDB-4411745	na
6/15/2005	Information Amendment	na	New Protocol; New Investigators	R092670-PSY-3005	087	4416120	EDMS-PSDB-4416120	na
6/15/2005	Information Amendment	na	New Protocol; New Investigators	R092670-PSY-1001	088	4414564	EDMS-PSDB-4414564	na
6/15/2005	Safety Report	na	NL-JNJFOC-20050402753 F-2	PALIOROS-P01-1011	089	4421835	EDMS-PSDB-4421865	na
6/16/2005	Safety Report	na	US-JNJFOC-20041201617 F-1	R076477-SCH-301	090	4424386	EDMS-PSDB-4424386	na
6/17/2005	Safety Report	na	US-JNJFOC-20050103392 F-3	R076477-SCH-301	091	4431011	EDMS-PSDB-4431011	na
6/23/2005	Safety Report	na	US-JNJFOC-20050603607 Initial	R076477-SCH-705	092	4441911	EDMS-PSDB-4441911	na
6/28/2005	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-1004	093	4460769	EDMS-PSDB-4460769	na
6/29/2005	Protocol Amendment	na	New Investigators	R092670-PSY-1004	094	4465586	EDMS-PSDB-4465586	na
7/1/2005	Safety Report	na	US-JNJFOC-20050304957 F-2	R076477-SCH-1009	095	4477198	EDMS-PSDB-4477198	na
7/6/2005	Safety Report	na	IN-JNJFOC-20050503897 F-2	R076477-SCH-301	096	4482015	EDMS-PSDB-4482015	na
7/6/2005	Safety Report	na	US-JNJFOC-20050603607 F-1	R076477-SCH-705	097	4484198	EDMS-PSDB-4484198	na
7/15/2005	Safety Report	na	MY-JNJFOC-20041204460 F-4	R076477-SCH-705	098	4520333	EDMS-PSDB-4520333	na
7/19/2005	IND Amendment	na	Investigator's Brochure: Agenda	na	099	4525548	EDMS-PSDB-4525548	na
7/20/2005	Safety Report	na	MY-JNJFOC-20041204460 F-5	R076477-SCH-705	100	4529100	EDMS-PSDB-4529100	na
7/21/2005	Information Amendment	na	CM&C	na	101	4531527	EDMS-PSDB-4531527	na
7/26/2005	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-1002	102	4544136	EDMS-PSDB-4544136	na
8/1/2005	IND Amendment	na	Request for Review of Revised Drug Product Registration Stability Protocol	na	103	4565568	EDMS-PSDB-4565568	na
8/5/2005	Annual Report	na	Reporting Period: 06/07/04 - 06/06/05	na	104	4574605	EDMS-PSDB-4574605	na
8/5/2005	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-1002	105	4586146	EDMS-PSDB-4586146	na
9/9/2005	Record of Contact	na	FDA Acceptance of Amended Drug Production Registration Stability Protocol for F013	na	na	4692158	EDMS-PSDB-4692158	na
9/26/2005	FDA Correspondence	na	Fax: Report to FDA from Sterling IRB	R092670-PSY-3004	na	4758438	EDMS-PSDB-4758438	na
9/27/2005	Record of Contact	9/26/2005	Report Received from Sterling IRB Regarding CBH Health LLC	na	na	4821292	EDMS-PSDB-4821292	na
9/29/2005	General Correspondence	na	J. Martynowicz is Now Primary Contact	na	106	4762944	EDMS-PSDB-4762944	na
9/30/2005	Protocol Amendment	na	New Investigators	R092670-PSY-1004	107	4764829	EDMS-PSDB-4764829	na
9/30/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3004	108	4771325	EDMS-PSDB-4771325	na
10/26/2005	Safety Report	na	RO-JNJFOC20050201375 F-2	R076477-SCH-301	109	4867147	EDMS-PSDB-4867147	na
11/11/2005	Safety Report	na	CA-JNJFOC-20051101512 Initial	R076477-SCH-705	110	4925304	EDMS-PSDB-4925304	na
11/21/2005	Safety Report	na	CA-JNJFOC-20051101512 F-1	R076477-SCH-705	111	4951293	EDMS-PSDB-4951293	na
11/29/2005	IND Amendment	na	Request for Review of Revised Drug Product Registration Stability Protocol	na	112	4966845	EDMS-PSDB-4966845	na
12/20/2005	Record of Contact	12/7/2005	Minutes of the 12/7/05 Bipolar I Disorder End-of-Phase 2/Pre-Phase 3 Meeting	na	na	5019672	EDMS-PSDB-5019672	na
12/21/2005	General Correspondence	na	Minutes of the 12/7/05 End of Phase 2 Meeting	na	113	5029714	EDMS-PSDB-5029714	na
12/22/2005	Safety Report	na	CA-JNJFOC-20051101512 F-2	R076477-SCH-705	114	5030729	EDMS-PSDB-5030729	na
12/29/2005	Safety Report	na	CA-JNJFOC-20051101512 F-3	R076477-SCH-705	115	5040289	EDMS-PSDB-5040289	na
2/2/2006	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-3002	116	5131076	EDMS-PSDB-5131076	na
2/23/2006	Protocol Amendment	na	New Investigators	R092670-PSY-3004	117	5205422	EDMS-PSDB-5205422	na

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3/6/2006	General Correspondence	na	IRB Waiver Request	na	118	5248420	EDMS-PSDB-5248420	na
3/24/2006	Safety Report	na	IN-JNJFOC-20060205306 7/15 Day Initial	R076477-SCH-701	119	5324478	EDMS-PSDB-5324478	na
3/24/2006	General Correspondence	na	Fax: IN-JNJFOC-20060205306 7/15 Day Initial	R076477-SCH-701	119	5358805	EDMS-PSDB-5358805	na
3/27/2006	Information Amendment	na	Clinical: Statistical Analysis Plan for R096270-PSY-3004	R092670-PSY-3004	120	5330146	EDMS-PSDB-5330146	na
4/3/2006	General Correspondence	na	Fax: IN-JNJFOC-20060205306 7/15 Day F-1	R076477-SCH-701	121	5352966	EDMS-PSDB-5352966	na
5/26/2006	FDA Correspondence	na	Letter: IRB Waiver Request Granted (S-117)	R092670-PSY-3004	na	5546925	EDMS-PSDB-5546925	na
5/26/2006	FDA Correspondence	na	Email/Attachment: IRB Wavier Request Granted (S-117)	R092670-PSY-3004	na	5545009	EDMS-PSDB-5545009	na
6/20/2006	IND Amendment	na	Protocol R092670-PSY-3003 Medication Kit Error	R092670-PSY-3003	122	5593354	EDMS-PSDB-5593354	na
6/26/2006	Information Amendment	na	Clinical: Statistical Analysis Plan for R096270-PSY-3003	R092670-PSY-3003	123	5617192	EDMS-PSDB-5617192	na
6/27/2006	Record of Contact	6/23/2006	DSI Notification of Study Compliance Deficiencies	na	na	6380254	EDMS-PSDB-6380254	na
7/11/2006	Information Amendment	na	Clinical	R092670-PSY-3001; R092670-PSY-3002; R092670-PSY-1004	124	5645851	EDMS-PSDB-5645851	na
7/12/2006	Safety Report	na	IN-JNJFOC-20060205306 F-2	R076477-SCH-701	125	5662755	EDMS-PSDB-5662755	na
7/17/2006	FDA Correspondence	na	Email/Attachment: Poland Investigator Site Audit with CL for SN 124	R092670-PSY-3001; R092670-PSY-3002; R092670-PSY-1004	na	5704533	EDMS-PSDB-5704533	na
7/21/2006	FDA Correspondence	na	Email: SAP for R092670-PSY-3003	R092670-PSY-3003	na	5714883	EDMS-PSDB-5714883	na
7/31/2006	FDA Correspondence	na	Email: FDA Response to Statistical Questions from 6/26/06	na	na	6033820	EDMS-PSDB-6033820	na
8/10/2006	IND Amendment	na	Investigator's Brochure: Addendum	na	126	5755623	EDMS-PSDB-5755623	na
8/14/2006	IND Amendment	na	Gen Corr: Request for Type B Pre-Phase 3 Meeting	na	127	5765064	EDMS-PSDB-5765064	na
8/17/2006	FDA Correspondence	na	Email: Secure E-Mail	na	na	5799979	EDMS-PSDB-5799979	na
9/1/2006	IND Amendment	na	Gen Corr: Request for Type C Meeting	na	128	5827016	EDMS-PSDB-5827016	na
9/6/2006	Safety Report	na	IN-JNJFOC-20060805629 Initial	R076477-BIM-3002	129	5838723	EDMS-PSDB-5838723	na
9/12/2006	FDA Correspondence	na	Email/Attachment: Meeting Request	na	na	5922314	EDMS-PSDB-5922314	na
9/18/2006	Annual Report	na	Reporting Period: 06/07/05 - 06/06/06	na	130	5868840	EDMS-PSDB-5868840	na
9/20/2006	FDA Correspondence	na	Email: Electronic Submissions	na	na	5922383	EDMS-PSDB-5922383	na
9/21/2006	General Correspondence	na	Request for Special Protocol Assessment	R076477-SCA-3003	131	5895887	EDMS-PSDB-5895887	na
9/22/2006	FDA Correspondence	na	Email: Meeting Granted	na	na	5922505	EDMS-PSDB-5922505	na
9/22/2006	FDA Correspondence	na	Email: Bipolar & Schizophrenia Meeting Requests	na	na	5922449	EDMS-PSDB-5922449	na
9/25/2006	FDA Correspondence	na	Email: Bipolar & Schizophrenia Meeting Requests	na	na	5922559	EDMS-PSDB-5922559	na
9/26/2006	FDA Correspondence	na	Email: Meeting Granted (12:08pm)	na	na	5922643	EDMS-PSDB-5922643	na
9/26/2006	FDA Correspondence	na	Email: Meeting Granted (3:22pm)	na	na	5922614	EDMS-PSDB-5922614	na
9/26/2006	Safety Report	na	IN-JNJFOC-20060805629 F-1	R076477-BIM-3002	132	5908836	EDMS-PSDB-5908836	na
10/6/2006	General Correspondence	na	eCTD Submission Conversion	na	133	0000	GW eCTD TOC	na
10/11/2006	Safety Report	na	IN-JNJFOC-20060205306 7/15 Day F-3	R076477-SCH-701	134	0134	GW eCTD TOC	na
10/18/2006	Safety Report	na	IN-JNJFOC-20060805629 F-2	R076477-BIM-3002	135	0135	GW eCTD TOC	na
10/27/2006	FDA Correspondence	na	Email: Transfer of Regulatory Responsibility	na	na	6027759	EDMS-PSDB-6027759	na
11/3/2006	FDA Correspondence	na	Letter: RFI in Response to 9/21/06 Request for Special Protocol Assessment	na	na	6058010	EDMS-PSDB-6058010	na
11/6/2006	Information Amendment	na	Clinical; Statistical Analysis Plan for PSY-3001	R092670-PSY-3001	136	0136	GW eCTD TOC	na
11/9/2006	General Correspondence	na	Briefing Pkg. For 12/11/06 Type C Meeting	na	137	0137	GW eCTD TOC	na
11/27/2006	Safety Report	na	IN-JNJFOC-20060805629 F-3	R076477-BIM-3002	138	0138	GW eCTD TOC	na
12/4/2006	FDA Correspondence	na	Email: N136 Stats Comments	na	na	6159463	EDMS-PSDB-6159463	na
12/7/2006	FDA Correspondence	na	Email/Attachment: N136 Stats Comments	R092670-PSY-3001	na	6163931	EDMS-PSDB-6163931	na
12/8/2006	Safety Report	na	SE-JNJFOC-20061005337 I	R092670-PSY-3002	139	0139	GW eCTD TOC	na
12/18/2006	Safety Report	na	Multiple (9)	Multiple	140	0140	GW eCTD TOC	na
12/18/2006	Safety Report	na	DE-JNJFOC-20061200532 I	R076477-BIM-3004	141	0141	GW eCTD TOC	na
12/19/2006	Information Amendment	na	Clinical: Statistical Analysis Plan for R092670-PSY-3001	R092670-PSY-3001	142	0142	GW eCTD TOC	na
12/21/2006	Record of Contact	12/11/2006	Minutes from the Meeting with the FDA Division of Psychiatry Products on 12/11/06	na	na	6218032	EDMS-PSDB-6218032	na
12/22/2006	Protocol Amendment	na	Statistical Analysis Plan for R092670-PSY-3005	R092670-PSY-3005	143	0143	GW eCTD TOC	na

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
12/27/2006	IND Amendment	na	Minutes of December 11, 2006 Type C Meeting	na	144	0144	GW eCTD TOC	na
12/29/2006	FDA Correspondence	na	Letter: Official Meeting Minutes from 12/11/06 Telecon	na	na	6248267	EDMS-PSDB-6248267	na
1/3/2007	FDA Correspondence	na	Email/Attachment: Official Meeting Minutes from 12/11/06 Telecon	na	na	6241885	EDMS-PSDB-6241885	na
1/4/2007	Protocol Amendment	na	New Protocol	R092670-PSY-3007	145	0145	GW eCTD TOC	na
1/9/2007	General Correspondence	na	Request for Type B Pre-Phase 3 Meeting	na	146	0146	GW eCTD TOC	na
1/9/2007	FDA Correspondence	na	Email/Attachment: Meeting Request, Paliperidone Palmitate Bipolar Development Program	na	na	6264901	EDMS-PSDB-6264901	na
1/19/2007	FDA Correspondence	na	Email: Plan to Stop Study R092670-PSY-3001	R092670-PSY-3001	na	6308521	EDMS-PSDB-6308521	na
1/23/2007	Record of Contact	na	FDA Div. Of Scientific Affairs: Telephone Contact Memo Between FDA and Local Trial Manager in Global Clinical Operations	R092670-PSY-3001	na	6360613	EDMS-PSDB-6360613	na
1/24/2007	General Correspondence	na	Response to RFI: Copy of Protocol R092670-PSY-3001	R092670-PSY-3001	na	6324934	EDMS-PSDB-6324934	na
1/26/2007	Protocol Amendment	na	Notification of PSY-3001 Study Termination Due to Efficacy; Change in Protocol R092670-PSY-3001; Final Statistical Analysis Plan for R092670-PSY-3001	R092670-PSY-3001	147	0147	GW eCTD TOC	na
1/31/2007	General Correspondence	na	IRB Waiver Request	R092670-PSY-3007	148	0148	GW eCTD TOC	na
2/2/2007	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-3006	149	0149	GW eCTD TOC	na
2/6/2007	IND Amendment	na	IRB Waiver Request	R092670-PSY-3006	150	0150	GW eCTD TOC	na
2/11/2007	Record of Contact	2/6/2007	GCP Violations at Dr. Chaganiti's Site Under Protocol R092670-PSY-3001	R092670-PSY-3001	na	6383191	EDMS-PSDB-6383191	na
2/12/2007	General Correspondence	na	Response to RFI from DSI: Protocol R092670-PSY-3001 Site Closure: MedClin Research, Inc.	R092670-PSY-3001	151	0151	GW eCTD TOC	na
2/15/2007	Safety Report	na	US-JNJFOC020070201813 Initial	R076477-SCA-3002	152	0152	GW eCTD TOC	na
2/16/2007	General Correspondence	na	Request for a Type B, Pre-NDA Meeting	na	153	0153	GW eCTD TOC	na
2/16/2007	FDA Correspondence	na	Fax/Attachment: 7/15 Day Safety Report (K.Kiedrow)	na	154	6416129	EDMS-PSDB-6416129	na
2/16/2007	FDA Correspondence	na	Fax/Attachment: 7/15 Day Safety Report (D.Bates)	na	154	6415933	EDMS-PSDB-6415933	na
2/16/2007	Safety Report	na	US-JNJFOC-20070203055 Initial 7/15 Day Report	R076477-BIM-3004	154	154	GW eCTD TOC	na
2/22/2007	FDA Correspondence	na	Email: 4/18/07 Type B Meeting Request Granted	na	na	6429676	EDMS-PSDB-6429676	na
2/26/2007	Safety Report	na	US-JNJFOC-20070204832 Initial	R076477-SCA-3001	155	0155	GW eCTD TOC	na
2/26/2007	Safety Report	na	Fax: US-JNJFOC-20070204832 Initial	R076477-SCA-3001	155	6446121	EDMS-PSDB-6446121	na
2/26/2007	FDA Correspondence	na	Letter: IRB Waiver Granted for 2/6/07 SN 150 Submission	R092670-PSY-3006	na	6452312	EDMS-PSDB-6452312	na
2/26/2007	FDA Correspondence	na	Letter: IRB Waiver Granted for 1/31/07 SN 148 Submission	R092670-PSY-3007	na	6526103	EDMS-PSDB-6526103	na
2/28/2007	Safety Report	na	US-JNJFOC-20070203055 F-1	R076477-BIM-3004	156	0156	GW eCTD TOC	na
3/5/2007	Safety Report	na	US-JNJFOC-20070204832 F-1	R076477-SCA-3001	157	0157	GW eCTD TOC	na
3/8/2007	Protocol Amendment	na	New Investigator	R092670-PSY-3007	158	0158	GW eCTD TOC	na
3/9/2007	Protocol Amendment	na	New Investigator	R092670-PSY-3006	159	0159	GW eCTD TOC	na
3/15/2007	IND Amendment	na	Briefing Package for 4/18/07 Type B Pre-NDA Meeting	na	160	0160	GW eCTD TOC	na
3/20/2007	Safety Report	na	US-JNJFOC-20070204832 F-2	R076477-SCA-3001	161	0161	GW eCTD TOC	na
3/22/2007	Protocol Amendment	na	Change in Protocol and Statistical Analysis Plan	R092670-PSY-3002	162	0162	GW eCTD TOC	na
3/26/2007	General Correspondence	na	Request for a Type B CMC/Biopharmaceutics Pre-NDA Meeting	na	163	0163	GW eCTD TOC	na
3/28/2007	Information Amendment	na	Clinical	na	164	0164	GW eCTD TOC	na
3/30/2007	Protocol Amendment	na	New and Updated Investigators	R092670-PSY-3007	165	0165	GW eCTD TOC	na
3/30/2007	FDA Correspondence	na	Email: Request for Submission Information	na	na	6614450	EDMS-PSDB-6614450	na
4/5/2007	FDA Correspondence	na	Email: SN 162 SAP - Question about Submission Study	R092670-PSY-3002	na	6637219	EDMS-PSDB-6637219	na
4/6/2007	General Correspondence	na	Response to FDA RFI: Additional Safety Information	na	166	0166	GW eCTD TOC	na
4/9/2007	FDA Correspondence	na	Email: Reply to FDS's 4/5/07 Study Question	R092670-PSY-3002	na	6637270	EDMS-PSDB-6637270	na
4/11/007	FDA Correspondence	na	Email: S/162 SAP	na	na	na	04-11-07 Email	na
4/16/2007	Safety Report	na	RO-JNJFOC-20060503643 F-1	R092670-PSY-3001	167	0167	GW eCTD TOC	na
4/17/2007	Safety Report	na	US-JNJFOC020070203055 F-2	R076477-BIM-3004	168	0168	GW eCTD TOC	na
4/19/2007	Safety Report	na	US-JNJFOC-20070401462 Initial	R076477-BIM-3002	169	0169	GW eCTD TOC	na

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
4/24/2007	FDA Correspondence	na	Email: Meeting Granted & Request for Meeting Pkg. By 5/10/07 S/163	na	na	6733756	EDMS-PSDB-6733756	na
4/25/2007	Safety Report	na	DE-JNJFOC-20061200532 F-1	R076477-BIM-3004	170	0170	GW eCTD TOC	na
4/30/2007	Safety Report	na	US-JNJFOC-20070405377 7-Day Initial	R076477-BIM-3004	171	0171	GW eCTD TOC	na
4/30/2007	FDA Correspondence	na	Fax: SN 171	na	na	6793658	EDMS-PSDB-6793658	na
4/30/2007	FDA Correspondence	na	Fax: SN 171 (2nd sending of fax)	na	na	6793660	EDMS-PSDB-6793660	na
5/3/2007	FDA Correspondence	na	Letter: 04/18/07 Official Meeting Minutes S/153	na	na	6801969	EDMS-PSDB-6801969	na
5/4/2007	Safety Report	na	US-JNJFOC-20070405377 7-Day F-1	R076477-BIM-3004	172	0172	GW eCTD TOC	na
5/4/2007	Safety Report	na	US-JNJFOC-20070404476 Initial	R076477-BIM-3001	173	0173	GW eCTD TOC	na
5/7/2007	Safety Report	na	US-JNJFOC-20070405377 7-Day F-2	R076477-BIM-3004	174	0174	GW eCTD TOC	na
5/8/2007	Safety Report	na	US-JNJFOC-20070404476 F-1	R076477-BIM-3001	175	0175	GW eCTD TOC	na
5/7/2007	FDA Correspondence	na	Email/Attachment: 04/18/07 Meeting Minutes S/153	na	na	6806260	EDMS-PSDB-6806260	na
5/9/2007	General Correspondence	na	Briefing Package for 6/7/07 CMC/Biopharmaceutics Type B pre-NDA Meeting	na	176	0176	GW eCTD TOC	na
5/9/2007	Safety Report	na	US-JNJFOC-20070204832 F-3	R076477-SCA-3001	177	0177	GW eCTD TOC	na
5/9/2007	FDA Correspondence	na	Letter: 1/4/07 SN 145 Statistical Review with Comments	R092670-PSY-3007	na	na	05-09-07 Letter	na
5/11/2007	General Correspondence	na	Minutes of the 4/18/07 Pre-NDA Meeting	na	178	0178	GW eCTD TOC	na
5/16/2007	Safety Report	na	US-JNJFOC020070201813 F-1	R076477-SCA-3002	179	0179	GW eCTD TOC	na
5/22/2007	Safety Report	na	US-JNJFOC-20070204832 F-4	R076477-SCA-3001	180	0180	GW eCTD TOC	na
5/24/2007	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-3006	181	0181	GW eCTD TOC	na
5/25/2007	Information Amendment	na	Nonclinical Pharmacology Study Report	na	182	0182	GW eCTD TOC	na
6/4/2007	FDA Correspondence	na	Email/Attachment: Preliminary Comments for 6/7/07 Meeting	na	na	na	06-04-07 Email	na
6/8/2007	Record of Contact	6/8/2007	Protocol PSY-3001 "Rater" Qualifications	R092670-PSY-3001	na	6963412	EDMS-PSDB-6963412	na
6/8/2007	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-3007	183	0183	GW eCTD TOC	na
6/14/2007	Protocol Amendment	na	New Protocol	R092670-PSY-1008	184	0184	GW eCTD TOC	na
6/15/2007	General Correspondence	na	IRB Waiver Request	R092670-PSY-1008	185	0185	GW eCTD TOC	na
6/15/2007	FDA Correspondence	na	Email: IND 67,356 3-Month Product Formulation: IND 76,952	na	na	na	06-15-07 Email	na
6/29/2007	FDA Correspondence	na	Letter: 06/07/07 Official Meeting Minutes	na	na	na	06-29-07 Letter	na
7/31/2007	Protocol Amendment	na	Change in Protocol	R092670-PSY-3006	186	0186	GW eSIG TOC	na
8/1/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3007	187	0187	GW eSIG TOC	na
8/13/2007	General Correspondence	na	Clarification of Official Minutes of the 07 June 2007 Meeting - CMC & Biopharmaceutics pre-NDA	na	188	0188	GW eSIG TOC	na
8/21/2007	Safety Report	na	DE-JNJFOC-20061200532 F-2	R076477-BIM-3004	189	0189	GW eSIG TOC	na
8/27/2007	General Correspondence	na	Sample Dataset Submission for IT Testing	na	190	0190	GW eSIG TOC	na
9/12/2007	FDA Correspondence	na	Email: Paliperidone palmitate NDA Submission Plans	na	na	na	09-12-07 Email	na
9/19/2007	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-1008	191	0191	GW eSIG TOC	na
9/20/2007	Annual Report	na	Reporting Period: 07/20/06 - 07/19/07	na	192	0192	GW eSIG TOC	na
11/1/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3007	193	0193	GW eSIG TOC	na
11/2/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3006	194	0194	GW eSIG TOC	na
11/29/2007	Safety Report	na	DE-JNJFOC-20061200532 F-3	R076477-BIM-3004	195	0195	GW eSIG TOC	na
12/6/2007	Record of Contact	6/16/2004	Minutes of June 16,2004 CMC/Biopharmaceutics End of Phase 2 Meeting for Paliperidon Palmitate	na	na	na	12-06-07 Email	na
12/11/2007	Information Amendment	na	CMC Drug Substance, Drug Product and Stability Data	na	196	0196	GW eSIG TOC	na
12/21/2007	General Correspondence	na	Request for Proposed Proprietary Name Review	na	197	0197	GW eSIG TOC	na
12/27/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3006	198	0198	GW eSIG TOC	na
1/9/2008	Information Amendment	na	Pharmacology/Toxicology	na	199	0199	GW eSIG TOC	na
1/15/2008	Protocol Amendment	na	New Investigators	R092670-PSY-3007	200	0200	GW eSIG TOC	na
1/23/2008	Protocol Amendment	na	Statistical Analysis Plan for R092670-PSY-3007	R092670-PSY-3007	201	0201	GW eSIG TOC	na
1/25/2008	General Correspondence	na	Postmarketing Study Commitment Final Report: Developmental Toxicity Study in the Rat Final Report	na	202	0202	GW eSIG TOC	na
1/30/2008	FDA Correspondence	na	Email/Attachment: IRB Waiver Granted	na	na	na	01-30-08 Email	na
2/1/2008	Protocol Amendment	na	New Investigators	R092670-PSY-1008	203	0203	GW eSIG TOC	na

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
2/8/2008	FDA Correspondence	na	Fax: SN 0204	na	na	na	02-08-08 Fax	na
2/8/2008	Safety Report	na	RU-JNJFOC-20070701878 Initial	R092670-PSY-3007	204	0204	GW eSIG TOC	na
2/28/2008	Protocol Amendment	na	New Investigators	R092670-PSY-3006	205	0205	GW eSIG TOC	na
2/28/2008	Protocol Amendment	na	New Investigators	R092670-PSY-3007	206	0206	GW eSIG TOC	na
3/19/2008	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-3006	207	0207	GW eSIG TOC	na
3/21/2008	Safety Report	na	US-JNJFOC-20070204832	R076477-SCA-3001	208	0208	GW eSIG TOC	na
4/9/2008	FDA Correspondence	na	Email: SN 201 Study R092670-PSY-3007 Statistical Analysis Plan	R092670-PSY-3007	na	na	04-09-08 Email	na
4/21/2008	Protocol Amendment	na	Change in Protocol	R092670-PSY-1008	209	0209	GW eSIG TOC	na
4/21/2008	Information Amendment	na	CMC	na	209	0209	GW eSIG TOC	na
4/28/2008	FDA Correspondence	na	Email/Attachment: Statistical Analysis Plan	R092670-PSY-3007	na	na	04-28-08 Email	na
7/14/2008	FDA Correspondence	na	Email/Attachments: Study Question	na	na	na	07-14-08 Email	na
7/25/2008	Safety Report	na	US-JNJFOC-20080704122 Initial	R076477-PSZ-3001	210	0210	GW eSIG TOC	na
8/1/2008	General Correspondence	na	Type B End-of-Phase 2/Pre-Phase 3 Meeting Request	na	211	0211	GW eSIG TOC	na
8/11/2008	Safety Report	na	IN-JNJFOC-20080704122 F-1	R076477-PSZ-3001	212	0212	GW eSIG TOC	na
8/25/2008	Safety Report	na	IN-JNJFOC-20080704122 F-1	R076477-PSZ-3001	213	0213	GW eSIG TOC	na
8/29/2008	General Correspondence	na	Briefing Package for 7 Oct 2008 Type B End-of-Phase 2/Pre-Phase 3 Meeting	na	214	0214	GW eSIG TOC	na
Note: Effective 09/01/08, emails and ROCs are only available electronically.								na
9/16/2008	Protocol Amendment	na	Change in Protocol	R092670-PSY-1008	215	0215	GW eSIG TOC	na
9/19/2008	Annual Report	na	Reporting Period: 07/20/07 - 07/19/08	na	216	0216	GW eSIG TOC	na
9/23/2008	Safety Report	na	IN-JNJFOC-20070201813 F-2	R076477-SCA-3002	217	0217	GW eSIG TOC	na
9/24/2008	General Correspondence	na	Updated Clinical Protocol Summary for 07Oct2008 Type C Meeting	na	218	0218	GW eSIG TOC	na
9/30/2008	FDA Correspondence	na	Preliminary Comments for Oct 7 Meeting	na	na	na	09-30-08 Email	na
10/16/2008	FDA Correspondence	na	Email/Attachments: Paliperidone palmitate Meeting Minutes	na	na	na	10-16-08 Email	na
10/31/2008	General Correspondence	na	Minutes of the 7Oct08 End of Phase 2/Pre-Phase 3 Mtg.	na	219	0219	GW eSIG TOC	na
2/19/2009	Safety Report	na	DE-JNJFOC-20061200532 F-4	R076477-BIM-3004	220	0220	GW eSIG TOC	67356-0220_eSIG
3/4/2009	IND Amendment	na	Updated Investigator's Brochure, Edition 9, 02/25/08	na	221	0221	GW eSIG TOC	67356-0221_eSIG
4/13/2009	Protocol Amendment	na	New Protocol	R092670-SCH-3004	222	0222	GW eSIG TOC	67356-0222_eSIG
4/13/2009	General Correspondence	na	Justification for Suicidality Assessment	na	222	0222	GW eSIG TOC	67356-0222_eSIG

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
5/6/2003	Original IND	na	Original IND (50 Volumes)	na	000	Multiple	Original IND	na
5/13/2007	Record of Contact	5/13/2003	Request for Additional Desk Copies and IND Number for Paliperidone palmitate	na	na	2651976	EDMS-PSDB-2651976	na
5/19/2003	Record of Contact	5/19/2003	Request for List of Nonclinical Studies Submitted Under IND 67,356	na	na	2656702	EDMS-PSDB-2656702	na
5/28/2003	General Correspondence	na	Response to Request by Review Chemist	na	001	2676686	EDMS-PSDB-2676686	na
5/30/2003	General Correspondence	na	Response to Request from Dr. Lois Freed	na	002	2683477	EDMS-PSDB-2683477	na
6/2/2003	Record of Contact	6/2/2003	Clearance to Proceed with the Studies Under IND	na	na	2697285	EDMS-PSDB-2697285	na
6/5/2003	General Correspondence	na	Response to Request by Review Chemist	na	003	2716903	EDMS-PSDB-2716903	na
9/11/2003	Protocol Amendment	na	New Investigators	R092670-USA-3	004	2931978	EDMS-PSDB-2931978	na
9/12/2003	Information Amendment	na	CMC; Pharmacology/Toxicology	na	005	2937288	EDMS-PSDB-2937288	na
10/28/2003	Protocol Amendment	na	New Protocol; New Investigator	R092670-SCH-201	006	3044512	EDMS-PSDB-3044512	na
1/9/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	007	3195694	EDMS-PSDB-3195694	na
1/23/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	008	3230681	EDMS-PSDB-3230681	na
2/11/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	009	3288697	EDMS-PSDB-3288697	na
3/31/2004	Safety Report	na	US-JNJFOC-20040304794 Initial	R076477-SCH-304	010	3397560	EDMS-PSDB-3397560	na
4/22/2004	General Correspondence	na	Request for Type B End of Phase 2 Meeting - Chemistry, Microbiology, and Biopharmaceutics	na	011	3442328	EDMS-PSDB-3442328	na
4/29/2004	FDA Correspondence	na	Letter: Meeting Request Granted for 6/16/04	na	na	3548304	EDMS-PSDB-3548304	na
5/6/2004	General Correspondence	na	Request for a Type B End-of-Phase 2 Meeting	na	012	3474299	EDMS-PSDB-3474299	na
5/10/2004	Safety Report	na	US-JNJFOC-20040304794 F-1	R076477-SCH-304	013	3479851	EDMS-PSDB-3479851	na
5/20/2004	General Correspondence	na	Briefing Package for 6/16/04 CMC/Biopharm Meeting	na	014	3514273	EDMS-PSDB-3514273	na
6/16/2004	Record of Contact	6/16/2004	Minutes of 6/16/04 CMC/Biopharmaceutics End of Phase 2 Meeting for Paliperidone palmitate	na	na	3594054	EDMS-PSDB-3594054	na
6/28/2004	General Correspondence	na	Minutes of 6/16/04 Type B End of Phase 2 Meeting - CMC/Biopharmceutics		015	3599384	EDMS-PSDB-3599384	na
7/1/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	016	3609437	EDMS-PSDB-3609437	na
8/4/2004	Annual Report	na	Reporting Period: 6/7/03 - 6/6/04	na	017	3681428	EDMS-PSDB-3681428	na
8/12/2004	Safety Report	na	IN-JNJFOC-20040800656 Initial	R076477-SCH-303	018	3699361	EDMS-PSDB-3699361	na
8/17/2004	Protocol Amendment	na	New Investigators	R092670-SCH-201	019	3704542	EDMS-PSDB-3704542	na
8/25/2004	Safety Report	na	IN-JNJFOC-20040800656 F-1	R076477-SCH-303	020	3723435	EDMS-PSDB-3723435	na
8/27/2004	General Correspondence	na	Notice of Intent to Request Special Protocol Assessment: Carcinogenicity	na	021	3728621	EDMS-PSDB-3728621	na
8/27/2004	FDA Correspondence	na	Fax: Notice of Intent to Request Special Protocol Assessment: Carcinogenicity SN 021	na	na	3732055	EDMS-PSDB-3732055	na
9/2/2004	FDA Correspondence	na	Letter: IND Acknowledgement Letter	na	na	3776556	EDMS-PSDB-3776556	na
9/9/2004	IND Amendment	na	Briefing Package for 9/28/04 End of Phase 2 Meeting	na	022	3756672	EDMS-PSDB-3756672	na
10/1/2004	IND Amendment	na	Request for Special Protocol Assessment: Carcnogenicity Protocol	na	023	3810109	EDMS-PSDB-3810109	na
10/26/2004	IND Amendment	na	Follow-up Information for Request for Special Protocol Assessment: Carcinogenicity Protocol	na	024	3860095	EDMS-PSDB-3860095	na
10/26/2004	Record of Contact	9/28/2004	Minutes of the 9/28/04 End of Phase 2 FDA Meeting	na	na	3818660	EDMS-PSDB-3818660	na
10/26/2004	FDA Correspondence	na	Fax: 10/26/04 Submission SN 024	na	na	3928067	EDMS-PSDB-3928067	na
10/27/2004	General Correspondence	na	Minutes of the 9/28/04 End of Phase 2 Meeting and Post-Meeting Follow-up Information	na	025	3862824	EDMS-PSDB-3862824	na
10/28/2004	General Correspondence	na	Response to FDA Request in 10/12/04 End of Phase 2 CMC/Biopharm Meeting Minutes	na	026	3868773	EDMS-PSDB-3868773	na
11/9/2004	Protocol Amendment	na	New Protocol; New Investigator	R076477-PSY-3004	027	3902895	EDMS-PSDB-3902895	na
11/10/2004	General Correspondence	na	Request for a Type C Meeting	na	028	3907677	EDMS-PSDB-3907677	na
11/11/2004	Safety Report	na	US-JNJFOC-20041100394 Initial	R092670-SCH-704	029	3909784	EDMS-PSDB-3909784	na
11/15/2004	FDA Correspondence	na	Fax: Response to Carcinogenicity Protocol Assessment Request - Final CAC Report	na	na	3928113	EDMS-PSDB-3928113	na

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11/18/2004	Information Amendment	na	CMC	na	030	3928878	EDMS-PSDB-3928878	na
11/22/2004	Safety Report	na	US-JNJFOC-20041102371 Initial	R076477-SCH-304	031	3931421	EDMS-PSDB-3931421	na
11/23/2004	Safety Report	na	US-JNJFOC-20041103584 Initial	R076477-SCH-304	032	3938295	EDMS-PSDB-3938295	na
11/23/2004	FDA Correspondence	na	Fax: Safety report SN 032	R076477-SCH-304	na	3961743	EDMS-PSDB-3961743	na
11/30/2004	Safety Report	na	US-JNJFOC-20041102371 F-1	R076477-SCH-304	033	3949874	EDMS-PSDB-3949874	na
11/30/2004	Information Amendment	na	Pharmacology/Toxicology; Clinical	na	034	3955196	EDMS-PSDB-3955196	na
12/2/2004	Safety Report	na	US-JNJFOC-20041103584 F-1	R076477-SCH-304	035	3961376	EDMS-PSDB-3961376	na
12/3/2004	Safety Report	na	MY-JNJFOC-20041105754 Initial	R076477-SCH-705	036	3963269	EDMS-PSDB-3963269	na
12/7/2004	Information Amendment	na	Pharmacology/Toxicology	na	037	3967273	EDMS-PSDB-3967273	na
12/10/2004	Safety Report	na	US-JNJFOC-20041201617 Initial	R076477-SCH-701	038	3976131	EDMS-PSDB-3976131	na
12/20/2004	Safety Report	na	IN-JNJFOC-20041202092 Initial	R076477-SCH-703	039	3998127	EDMS-PSDB-3998127	na
12/20/2004	General Correspondence	na	Briefing Package for 1/13/05 Meeting	na	040	3998804	EDMS-PSDB-3998804	na
12/23/2004	Safety Report	na	CA-JNJFOC-20041204345 Initial	R076477-SCH-305	041	4008929	EDMS-PSDB-4008929	na
12/23/2004	Safety Report	na	MY-JNJFOC-20041105754 F-1	R076477-SCH-705	042	4007899	EDMS-PSDB-4007899	na
12/27/2004	Safety Report	na	MY-JNJFOC-20041204460 Initial	R076477-SCH-705	043	4010952	EDMS-PSDB-4010952	na
12/27/2004	Safety Report	na	IN-JNJFOC-20041202092 F-1	R076477-SCH-703	044	4010959	EDMS-PSDB-4010959	na
12/27/2004	Safety Report	na	MY-JNJFOC-20041105754 F-2	R076477-SCH-705	045	4010966	EDMS-PSDB-4010966	na
1/4/2005	Safety Report	na	CA-NJFOC-20041204345 F-1	R076477-SCH-305	046	4019867	EDMS-PSDB-4019867	na
1/6/2005	Protocol Amendment	na	New Protocol; New Investigator	R092670-PSY-3001	047	4023920	EDMS-PSDB-4023920	na
1/7/2005	Safety Report	na	MY-JNJFOC-20041105754 F-3	R076477-SCH-705	048	4026257	EDMS-PSDB-4026257	na
1/14/2005	Safety Report	na	US-JNJFOC-20041100394 F-1	R076477-SCH-704	049	4042911	EDMS-PSDB-4042911	na
1/18/2005	Information Amendment	na	Pharmacology/Toxicology	na	050	4050521	EDMS-PSDB-4050521	na
1/18/2005	Safety Report	na	PL-JNJFOC-20041206244 Initial	R076477-SCH-703	051	4050379	EDMS-PSDB-4050379	na
1/19/2005	Safety Report	na	US-JNJFOC-20050103392 Initial	R076477-SCH-701	052	4056138	EDMS-PSDB-4056138	na
1/19/2005	FDA Correspondence	na	Fax: Safety Report SN 052	R076477-SCH-701	na	4063491	EDMS-PSDB-4063491	na
1/21/2005	Safety Report	na	US-JNJFOC-20050103392 F-1	R076477-SCH-701	053	4063195	EDMS-PSDB-4063195	na
1/24/2005	Safety Report	na	CA-JNJFOC-20041204345 F-2	R076477-SCH-305	054	4066354	EDMS-PSDB-4066354	na
1/26/2005	Safety Report	na	US-JNJFOC-20050103392 F-2	R076477-SCH-301	055	4070650	EDMS-PSDB-4070650	na
2/2/2005	Safety Report	na	US-JNJFOC-20050105338 Initial	R076477-SCH-305	056	4092677	EDMS-PSDB-4092677	na
2/2/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3004	057	4093088	EDMS-PSDB-4093088	na
2/3/2005	Safety Report	na	IN-JNJFOC-20041202092 F-2	R076477-SCH-703	058	4094614	EDMS-PSDB-4094614	na
2/4/2005	Safety Report	na	US-JNJFOC-20041100394 F-2	R076477-SCH-704	059	4098820	EDMS-PSDB-4098820	na
2/4/2005	Safety Report	na	MY-JNJFOC-20050105402 Initial	R076477-SCH-305	060	4098827	EDMS-PSDB-4098827	na
2/11/2005	Safety Report	na	RO-JNJFOC-20050201375 Initial	R076477-SCH-301	061	4115429	EDMS-PSDB-4115429	na
2/11/2005	FDA Correspondence	na	Fax: Safety Report SN 061	R076477-SCH-301	na	4140901	EDMS-PSDB-4140901	na
2/14/2005	Safety Report	na	US-JNJFOC-20050105338 F-1	R076477-SCH-305	062	4119644	EDMS-PSDB-4119644	na
2/17/2005	Safety Report	na	MY-JNJF)C-20050105402 F-1	R076477-SCH-305	063	4128519	EDMS-PSDB-4128519	na
2/22/2005	Safety Report	na	RO-JNJFOC-20050201375 F-1	R076477-SCH-301	064	4137747	EDMS-PSDB-4137747	na
3/23/2005	Safety Report	na	US-JNJFOC-20050304957 Initial	R076477-SCH-1009	065	4209442	EDMS-PSDB-4209442	na
3/23/2005	General Correspondence	na	Fax: Safety Report SN 065	R076477-SCH-1009	na	4210799	EDMS-PSDB-4210799	na
3/31/2005	Safety Report	na	US-JNJFOC-20050304957 F-1	R076477-SCH-1009	066	4224908	EDMS-PSDB-4224908	na
4/4/2005	Safety Report	na	TW-JNJFOC-20050305349 Initial	R076477-SCH-305	067	4233955	EDMS-PSDB-4233955	na
4/13/2005	Safety Report	na	MY-JNJFOC-20041204460 F-1	R076477-SCH-705	068	4255811	EDMS-PSDB-4255811	na
4/15/2005	Safety Report	na	MY-JNJFOC-20041204460 F-2	R076477-SCH-705	069	4259582	EDMS-PSDB-4259582	na
4/15/2005	Safety Report	na	NL-JNJFOC-20050402753 Initial	PALIOROS-SCH-1011	070	4267510	EDMS-PSDB-4267510	na
4/15/2005	General Correspondence	na	Fax: Safety Report SN 070	PALIOROS-SCH-1011	na	4278984	EDMS-PSDB-4278984	na
4/20/2005	Safety Report	na	US-JNJFOC-20050105338 F-2	R076477-SCH-305	071	4279747	EDMS-PSDB-4279747	na
4/20/2005	Safety Report	na	MY-JNJFOC-20041105754 F-4	R076477-SCH-705	072	4279761	EDMS-PSDB-4279761	na
4/20/2005	Safety Report	na	US-JNJFOC-20041100394 F-3	R076477-SCH-704	073	4279122	EDMS-PSDB-4279122	na
4/22/2005	Safety Report	na	NL-JNJFOC-20050402753 F-1	PALIOROS-SCH-1011	074	4287661	EDMS-PSDB-4287661	na
5/9/2005	IND Amendment	na	Reclassification of IND Safety Reports	na	075	4322913	EDMS-PSDB-4322913	na
5/9/2005	Protocol Amendment	na	New Protocol; New Investigator	R092670-PSY-3003	076	4322769	EDMS-PSDB-4322769	na

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5/10/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3004	077	4325611	EDMS-PSDB-4325611	na
5/11/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3001	078	4329282	EDMS-PSDB-4329282	na
5/16/2005	Safety Report	na	US-JNJFOC-20050502821 Initial	R076477-SCH-1009	079	4343153	EDMS-PSDB-4343153	na
5/16/2005	FDA Correspondence	na	Fax: Safety Report SN 079	R076477-SCH-1009	na	4348879	EDMS-PSDB-4348879	na
5/23/2005	Safety Report	na	MY-JNJFOC-20041204460 F-3	R076477-SCH-705	080	4354981	EDMS-PSDB-4354981	na
5/25/2005	Safety Report	na	IN-JNJFOC-20050503897 Initial	R076477-SCH-301	081	4362170	EDMS-PSDB-4362170	na
5/25/2005	Safety Report	na	IN-JNJFOC-20050503897 F-1	R076477-SCH-301	082	4381574	EDMS-PSDB-4381574	na
6/10/2005	Information Amendment	na	CM&C	R092670-PSY-3003	083	4403047	EDMS-PSDB-1103047	na
6/13/2005	General Correspondence	na	Request for Review of Drug Product Registration Stability Protocol	na	084	4411495	EDMS-PSDB-4411495	na
6/14/2005	Information Amendment	na	Change in Protocol	R092670-PSY-3001	085	4411736	EDMS-PSDB-4411736	na
6/14/2005	Information Amendment	na	Change in Protocol	R092670-PSY-3004	086	4411745	EDMS-PSDB-4411745	na
6/15/2005	Information Amendment	na	New Protocol; New Investigators	R092670-PSY-3005	087	4416120	EDMS-PSDB-4416120	na
6/15/2005	Information Amendment	na	New Protocol; New Investigators	R092670-PSY-1001	088	4414564	EDMS-PSDB-4414564	na
6/15/2005	Safety Report	na	NL-JNJFOC-20050402753 F-2	PALIOROS-P01-1011	089	4421835	EDMS-PSDB-4421865	na
6/16/2005	Safety Report	na	US-JNJFOC-20041201617 F-1	R076477-SCH-301	090	4424386	EDMS-PSDB-4424386	na
6/17/2005	Safety Report	na	US-JNJFOC-20050103392 F-3	R076477-SCH-301	091	4431011	EDMS-PSDB-4431011	na
6/23/2005	Safety Report	na	US-JNJFOC-20050603607 Initial	R076477-SCH-705	092	4441911	EDMS-PSDB-4441911	na
6/28/2005	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-1004	093	4460769	EDMS-PSDB-4460769	na
6/29/2005	Protocol Amendment	na	New Investigators	R092670-PSY-1004	094	4465586	EDMS-PSDB-4465586	na
7/1/2005	Safety Report	na	US-JNJFOC-20050304957 F-2	R076477-SCH-1009	095	4477198	EDMS-PSDB-4477198	na
7/6/2005	Safety Report	na	IN-JNJFOC-20050503897 F-2	R076477-SCH-301	096	4482015	EDMS-PSDB-4482015	na
7/6/2005	Safety Report	na	US-JNJFOC-20050603607 F-1	R076477-SCH-705	097	4484198	EDMS-PSDB-4484198	na
7/15/2005	Safety Report	na	MY-JNJFOC-20041204460 F-4	R076477-SCH-705	098	4520333	EDMS-PSDB-4520333	na
7/19/2005	IND Amendment	na	Investigator's Brochure: Agenda	na	099	4525548	EDMS-PSDB-4525548	na
7/20/2005	Safety Report	na	MY-JNJFOC-20041204460 F-5	R076477-SCH-705	100	4529100	EDMS-PSDB-4529100	na
7/21/2005	Information Amendment	na	CM&C	na	101	4531527	EDMS-PSDB-4531527	na
7/26/2005	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-1002	102	4544136	EDMS-PSDB-4544136	na
8/1/2005	IND Amendment	na	Request for Review of Revised Drug Product Registration Stability Protocol	na	103	4565568	EDMS-PSDB-4565568	na
8/5/2005	Annual Report	na	Reporting Period: 06/07/04 - 06/06/05	na	104	4574605	EDMS-PSDB-4574605	na
8/5/2005	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-1002	105	4586146	EDMS-PSDB-4586146	na
9/9/2005	Record of Contact	na	FDA Acceptance of Amended Drug Production Registration Stability Protocol for F013	na	na	4692158	EDMS-PSDB-4692158	na
9/26/2005	FDA Correspondence	na	Fax: Report to FDA from Sterling IRB	R092670-PSY-3004	na	4758438	EDMS-PSDB-4758438	na
9/27/2005	Record of Contact	9/26/2005	Report Received from Sterling IRB Regarding CBH Health LLC	na	na	4821292	EDMS-PSDB-4821292	na
9/29/2005	General Correspondence	na	J. Martynowicz is Now Primary Contact	na	106	4762944	EDMS-PSDB-4762944	na
9/30/2005	Protocol Amendment	na	New Investigators	R092670-PSY-1004	107	4764829	EDMS-PSDB-4764829	na
9/30/2005	Protocol Amendment	na	New Investigators	R092670-PSY-3004	108	4771325	EDMS-PSDB-4771325	na
10/26/2005	Safety Report	na	RO-JNJFOC20050201375 F-2	R076477-SCH-301	109	4867147	EDMS-PSDB-4867147	na
11/11/2005	Safety Report	na	CA-JNJFOC-20051101512 Initial	R076477-SCH-705	110	4925304	EDMS-PSDB-4925304	na
11/21/2005	Safety Report	na	CA-JNJFOC-20051101512 F-1	R076477-SCH-705	111	4951293	EDMS-PSDB-4951293	na
11/29/2005	IND Amendment	na	Request for Review of Revised Drug Product Registration Stability Protocol	na	112	4966845	EDMS-PSDB-4966845	na
12/20/2005	Record of Contact	12/7/2005	Minutes of the 12/7/05 Bipolar I Disorder End-of-Phase 2/Pre-Phase 3 Meeting	na	na	5019672	EDMS-PSDB-5019672	na
12/21/2005	General Correspondence	na	Minutes of the 12/7/05 End of Phase 2 Meeting	na	113	5029714	EDMS-PSDB-5029714	na
12/22/2005	Safety Report	na	CA-JNJFOC-20051101512 F-2	R076477-SCH-705	114	5030729	EDMS-PSDB-5030729	na
12/29/2005	Safety Report	na	CA-JNJFOC-20051101512 F-3	R076477-SCH-705	115	5040289	EDMS-PSDB-5040289	na
2/2/2006	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-3002	116	5131076	EDMS-PSDB-5131076	na
2/23/2006	Protocol Amendment	na	New Investigators	R092670-PSY-3004	117	5205422	EDMS-PSDB-5205422	na

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3/6/2006	General Correspondence	na	IRB Waiver Request	na	118	5248420	EDMS-PSDB-5248420	na
3/24/2006	Safety Report	na	IN-JNJFOC-20060205306 7/15 Day Initial	R076477-SCH-701	119	5324478	EDMS-PSDB-5324478	na
3/24/2006	General Correspondence	na	Fax: IN-JNJFOC-20060205306 7/15 Day Initial	R076477-SCH-701	119	5358805	EDMS-PSDB-5358805	na
3/27/2006	Information Amendment	na	Clinical: Statistical Analysis Plan for R096270-PSY-3004	R092670-PSY-3004	120	5330146	EDMS-PSDB-5330146	na
4/3/2006	General Correspondence	na	Fax: IN-JNJFOC-20060205306 7/15 Day F-1	R076477-SCH-701	121	5352966	EDMS-PSDB-5352966	na
5/26/2006	FDA Correspondence	na	Letter: IRB Waiver Request Granted (S-117)	R092670-PSY-3004	na	5546925	EDMS-PSDB-5546925	na
5/26/2006	FDA Correspondence	na	Email/Attachment: IRB Wavier Request Granted (S-117)	R092670-PSY-3004	na	5545009	EDMS-PSDB-5545009	na
6/20/2006	IND Amendment	na	Protocol R092670-PSY-3003 Medication Kit Error	R092670-PSY-3003	122	5593354	EDMS-PSDB-5593354	na
6/26/2006	Information Amendment	na	Clinical: Statistical Analysis Plan for R096270-PSY-3003	R092670-PSY-3003	123	5617192	EDMS-PSDB-5617192	na
6/27/2006	Record of Contact	6/23/2006	DSI Notification of Study Compliance Deficiencies	na	na	6380254	EDMS-PSDB-6380254	na
7/11/2006	Information Amendment	na	Clinical	R092670-PSY-3001; R092670-PSY-3002; R092670-PSY-1004	124	5645851	EDMS-PSDB-5645851	na
7/12/2006	Safety Report	na	IN-JNJFOC-20060205306 F-2	R076477-SCH-701	125	5662755	EDMS-PSDB-5662755	na
7/17/2006	FDA Correspondence	na	Email/Attachment: Poland Investigator Site Audit with CL for SN 124	R092670-PSY-3001; R092670-PSY-3002; R092670-PSY-1004	na	5704533	EDMS-PSDB-5704533	na
7/21/2006	FDA Correspondence	na	Email: SAP for R092670-PSY-3003	R092670-PSY-3003	na	5714883	EDMS-PSDB-5714883	na
7/31/2006	FDA Correspondence	na	Email: FDA Response to Statistical Questions from 6/26/06	na	na	6033820	EDMS-PSDB-6033820	na
8/10/2006	IND Amendment	na	Investigator's Brochure: Addendum	na	126	5755623	EDMS-PSDB-5755623	na
8/14/2006	IND Amendment	na	Gen Corr: Request for Type B Pre-Phase 3 Meeting	na	127	5765064	EDMS-PSDB-5765064	na
8/17/2006	FDA Correspondence	na	Email: Secure E-Mail	na	na	5799979	EDMS-PSDB-5799979	na
9/1/2006	IND Amendment	na	Gen Corr: Request for Type C Meeting	na	128	5827016	EDMS-PSDB-5827016	na
9/6/2006	Safety Report	na	IN-JNJFOC-20060805629 Initial	R076477-BIM-3002	129	5838723	EDMS-PSDB-5838723	na
9/12/2006	FDA Correspondence	na	Email/Attachment: Meeting Request	na	na	5922314	EDMS-PSDB-5922314	na
9/18/2006	Annual Report	na	Reporting Period: 06/07/05 - 06/06/06	na	130	5868840	EDMS-PSDB-5868840	na
9/20/2006	FDA Correspondence	na	Email: Electronic Submissions	na	na	5922383	EDMS-PSDB-5922383	na
9/21/2006	General Correspondence	na	Request for Special Protocol Assessment	R076477-SCA-3003	131	5895887	EDMS-PSDB-5895887	na
9/22/2006	FDA Correspondence	na	Email: Meeting Granted	na	na	5922505	EDMS-PSDB-5922505	na
9/22/2006	FDA Correspondence	na	Email: Bipolar & Schizophrenia Meeting Requests	na	na	5922449	EDMS-PSDB-5922449	na
9/25/2006	FDA Correspondence	na	Email: Bipolar & Schizophrenia Meeting Requests	na	na	5922559	EDMS-PSDB-5922559	na
9/26/2006	FDA Correspondence	na	Email: Meeting Granted (12:08pm)	na	na	5922643	EDMS-PSDB-5922643	na
9/26/2006	FDA Correspondence	na	Email: Meeting Granted (3:22pm)	na	na	5922614	EDMS-PSDB-5922614	na
9/26/2006	Safety Report	na	IN-JNJFOC-20060805629 F-1	R076477-BIM-3002	132	5908836	EDMS-PSDB-5908836	na
10/6/2006	General Correspondence	na	eCTD Submission Conversion	na	133	0000	GW eCTD TOC	na
10/11/2006	Safety Report	na	IN-JNJFOC-20060205306 7/15 Day F-3	R076477-SCH-701	134	0134	GW eCTD TOC	na
10/18/2006	Safety Report	na	IN-JNJFOC-20060805629 F-2	R076477-BIM-3002	135	0135	GW eCTD TOC	na
10/27/2006	FDA Correspondence	na	Email: Transfer of Regulatory Responsibility	na	na	6027759	EDMS-PSDB-6027759	na
11/3/2006	FDA Correspondence	na	Letter: RFI in Response to 9/21/06 Request for Special Protocol Assessment	na	na	6058010	EDMS-PSDB-6058010	na
11/6/2006	Information Amendment	na	Clinical; Statistical Analysis Plan for PSY-3001	R092670-PSY-3001	136	0136	GW eCTD TOC	na
11/9/2006	General Correspondence	na	Briefing Pkg. For 12/11/06 Type C Meeting	na	137	0137	GW eCTD TOC	na
11/27/2006	Safety Report	na	IN-JNJFOC-20060805629 F-3	R076477-BIM-3002	138	0138	GW eCTD TOC	na
12/4/2006	FDA Correspondence	na	Email: N136 Stats Comments	na	na	6159463	EDMS-PSDB-6159463	na
12/7/2006	FDA Correspondence	na	Email/Attachment: N136 Stats Comments	R092670-PSY-3001	na	6163931	EDMS-PSDB-6163931	na
12/8/2006	Safety Report	na	SE-JNJFOC-20061005337 I	R092670-PSY-3002	139	0139	GW eCTD TOC	na
12/18/2006	Safety Report	na	Multiple (9)	Multiple	140	0140	GW eCTD TOC	na
12/18/2006	Safety Report	na	DE-JNJFOC-20061200532 I	R076477-BIM-3004	141	0141	GW eCTD TOC	na
12/19/2006	Information Amendment	na	Clinical: Statistical Analysis Plan for R092670-PSY-3001	R092670-PSY-3001	142	0142	GW eCTD TOC	na
12/21/2006	Record of Contact	12/11/2006	Minutes from the Meeting with the FDA Division of Psychiatry Products on 12/11/06	na	na	6218032	EDMS-PSDB-6218032	na
12/22/2006	Protocol Amendment	na	Statistical Analysis Plan for R092670-PSY-3005	R092670-PSY-3005	143	0143	GW eCTD TOC	na

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
12/27/2006	IND Amendment	na	Minutes of December 11, 2006 Type C Meeting	na	144	0144	GW eCTD TOC	na
12/29/2006	FDA Correspondence	na	Letter: Official Meeting Minutes from 12/11/06 Telecon	na	na	6248267	EDMS-PSDB-6248267	na
1/3/2007	FDA Correspondence	na	Email/Attachment: Official Meeting Minutes from 12/11/06 Telecon	na	na	6241885	EDMS-PSDB-6241885	na
1/4/2007	Protocol Amendment	na	New Protocol	R092670-PSY-3007	145	0145	GW eCTD TOC	na
1/9/2007	General Correspondence	na	Request for Type B Pre-Phase 3 Meeting	na	146	0146	GW eCTD TOC	na
1/9/2007	FDA Correspondence	na	Email/Attachment: Meeting Request, Paliperidone Palmitate Bipolar Development Program	na	na	6264901	EDMS-PSDB-6264901	na
1/19/2007	FDA Correspondence	na	Email: Plan to Stop Study R092670-PSY-3001	R092670-PSY-3001	na	6308521	EDMS-PSDB-6308521	na
1/23/2007	Record of Contact	na	FDA Div. Of Scientific Affairs: Telephone Contact Memo Between FDA and Local Trial Manager in Global Clinical Operations	R092670-PSY-3001	na	6360613	EDMS-PSDB-6360613	na
1/24/2007	General Correspondence	na	Response to RFI: Copy of Protocol R092670-PSY-3001	R092670-PSY-3001	na	6324934	EDMS-PSDB-6324934	na
1/26/2007	Protocol Amendment	na	Notification of PSY-3001 Study Termination Due to Efficacy; Change in Protocol R092670-PSY-3001; Final Statistical Analysis Plan for R092670-PSY-3001	R092670-PSY-3001	147	0147	GW eCTD TOC	na
1/31/2007	General Correspondence	na	IRB Waiver Request	R092670-PSY-3007	148	0148	GW eCTD TOC	na
2/2/2007	Protocol Amendment	na	New Protocol; New Investigators	R092670-PSY-3006	149	0149	GW eCTD TOC	na
2/6/2007	IND Amendment	na	IRB Waiver Request	R092670-PSY-3006	150	0150	GW eCTD TOC	na
2/11/2007	Record of Contact	2/6/2007	GCP Violations at Dr. Chaganiti's Site Under Protocol R092670-PSY-3001	R092670-PSY-3001	na	6383191	EDMS-PSDB-6383191	na
2/12/2007	General Correspondence	na	Response to RFI from DSI: Protocol R092670-PSY-3001 Site Closure: MedClin Research, Inc.	R092670-PSY-3001	151	0151	GW eCTD TOC	na
2/15/2007	Safety Report	na	US-JNJFOC020070201813 Initial	R076477-SCA-3002	152	0152	GW eCTD TOC	na
2/16/2007	General Correspondence	na	Request for a Type B, Pre-NDA Meeting	na	153	0153	GW eCTD TOC	na
2/16/2007	FDA Correspondence	na	Fax/Attachment: 7/15 Day Safety Report (K.Kiedrow)	na	154	6416129	EDMS-PSDB-6416129	na
2/16/2007	FDA Correspondence	na	Fax/Attachment: 7/15 Day Safety Report (D.Bates)	na	154	6415933	EDMS-PSDB-6415933	na
2/16/2007	Safety Report	na	US-JNJFOC-20070203055 Initial 7/15 Day Report	R076477-BIM-3004	154	154	GW eCTD TOC	na
2/22/2007	FDA Correspondence	na	Email: 4/18/07 Type B Meeting Request Granted	na	na	6429676	EDMS-PSDB-6429676	na
2/26/2007	Safety Report	na	US-JNJFOC-20070204832 Initial	R076477-SCA-3001	155	0155	GW eCTD TOC	na
2/26/2007	Safety Report	na	Fax: US-JNJFOC-20070204832 Initial	R076477-SCA-3001	155	6446121	EDMS-PSDB-6446121	na
2/26/2007	FDA Correspondence	na	Letter: IRB Waiver Granted for 2/6/07 SN 150 Submission	R092670-PSY-3006	na	6452312	EDMS-PSDB-6452312	na
2/26/2007	FDA Correspondence	na	Letter: IRB Waiver Granted for 1/31/07 SN 148 Submission	R092670-PSY-3007	na	6526103	EDMS-PSDB-6526103	na
2/28/2007	Safety Report	na	US-JNJFOC-20070203055 F-1	R076477-BIM-3004	156	0156	GW eCTD TOC	na
3/5/2007	Safety Report	na	US-JNJFOC-20070204832 F-1	R076477-SCA-3001	157	0157	GW eCTD TOC	na
3/8/2007	Protocol Amendment	na	New Investigator	R092670-PSY-3007	158	0158	GW eCTD TOC	na
3/9/2007	Protocol Amendment	na	New Investigator	R092670-PSY-3006	159	0159	GW eCTD TOC	na
3/15/2007	IND Amendment	na	Briefing Package for 4/18/07 Type B Pre-NDA Meeting	na	160	0160	GW eCTD TOC	na
3/20/2007	Safety Report	na	US-JNJFOC-20070204832 F-2	R076477-SCA-3001	161	0161	GW eCTD TOC	na
3/22/2007	Protocol Amendment	na	Change in Protocol and Statistical Analysis Plan	R092670-PSY-3002	162	0162	GW eCTD TOC	na
3/26/2007	General Correspondence	na	Request for a Type B CMC/Biopharmaceutics Pre-NDA Meeting	na	163	0163	GW eCTD TOC	na
3/28/2007	Information Amendment	na	Clinical	na	164	0164	GW eCTD TOC	na
3/30/2007	Protocol Amendment	na	New and Updated Investigators	R092670-PSY-3007	165	0165	GW eCTD TOC	na
3/30/2007	FDA Correspondence	na	Email: Request for Submission Information	na	na	6614450	EDMS-PSDB-6614450	na
4/5/2007	FDA Correspondence	na	Email: SN 162 SAP - Question about Submission Study	R092670-PSY-3002	na	6637219	EDMS-PSDB-6637219	na
4/6/2007	General Correspondence	na	Response to FDA RFI: Additional Safety Information	na	166	0166	GW eCTD TOC	na
4/9/2007	FDA Correspondence	na	Email: Reply to FDS's 4/5/07 Study Question	R092670-PSY-3002	na	6637270	EDMS-PSDB-6637270	na
4/11/007	FDA Correspondence	na	Email: S/162 SAP	na	na	na	04-11-07 Email	na
4/16/2007	Safety Report	na	RO-JNJFOC-20060503643 F-1	R092670-PSY-3001	167	0167	GW eCTD TOC	na
4/17/2007	Safety Report	na	US-JNJFOC020070203055 F-2	R076477-BIM-3004	168	0168	GW eCTD TOC	na
4/19/2007	Safety Report	na	US-JNJFOC-20070401462 Initial	R076477-BIM-3002	169	0169	GW eCTD TOC	na

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
4/24/2007	FDA Correspondence	na	Email: Meeting Granted & Request for Meeting Pkg. By 5/10/07 S/163	na	na	6733756	EDMS-PSDB-6733756	na
4/25/2007	Safety Report	na	DE-JNJFOC-20061200532 F-1	R076477-BIM-3004	170	0170	GW eCTD TOC	na
4/30/2007	Safety Report	na	US-JNJFOC-20070405377 7-Day Initial	R076477-BIM-3004	171	0171	GW eCTD TOC	na
4/30/2007	FDA Correspondence	na	Fax: SN 171	na	na	6793658	EDMS-PSDB-6793658	na
4/30/2007	FDA Correspondence	na	Fax: SN 171 (2nd sending of fax)	na	na	6793660	EDMS-PSDB-6793660	na
5/3/2007	FDA Correspondence	na	Letter: 04/18/07 Official Meeting Minutes S/153	na	na	6801969	EDMS-PSDB-6801969	na
5/4/2007	Safety Report	na	US-JNJFOC-20070405377 7-Day F-1	R076477-BIM-3004	172	0172	GW eCTD TOC	na
5/4/2007	Safety Report	na	US-JNJFOC-20070404476 Initial	R076477-BIM-3001	173	0173	GW eCTD TOC	na
5/7/2007	Safety Report	na	US-JNJFOC-20070405377 7-Day F-2	R076477-BIM-3004	174	0174	GW eCTD TOC	na
5/8/2007	Safety Report	na	US-JNJFOC-20070404476 F-1	R076477-BIM-3001	175	0175	GW eCTD TOC	na
5/7/2007	FDA Correspondence	na	Email/Attachment: 04/18/07 Meeting Minutes S/153	na	na	6806260	EDMS-PSDB-6806260	na
5/9/2007	General Correspondence	na	Briefing Package for 6/7/07 CMC/Biopharmaceutics Type B pre-NDA Meeting	na	176	0176	GW eCTD TOC	na
5/9/2007	Safety Report	na	US-JNJFOC-20070204832 F-3	R076477-SCA-3001	177	0177	GW eCTD TOC	na
5/9/2007	FDA Correspondence	na	Letter: 1/4/07 SN 145 Statistical Review with Comments	R092670-PSY-3007	na	na	05-09-07 Letter	na
5/11/2007	General Correspondence	na	Minutes of the 4/18/07 Pre-NDA Meeting	na	178	0178	GW eCTD TOC	na
5/16/2007	Safety Report	na	US-JNJFOC020070201813 F-1	R076477-SCA-3002	179	0179	GW eCTD TOC	na
5/22/2007	Safety Report	na	US-JNJFOC-20070204832 F-4	R076477-SCA-3001	180	0180	GW eCTD TOC	na
5/24/2007	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-3006	181	0181	GW eCTD TOC	na
5/25/2007	Information Amendment	na	Nonclinical Pharmacology Study Report	na	182	0182	GW eCTD TOC	na
6/4/2007	FDA Correspondence	na	Email/Attachment: Preliminary Comments for 6/7/07 Meeting	na	na	na	06-04-07 Email	na
6/8/2007	Record of Contact	6/8/2007	Protocol PSY-3001 "Rater" Qualifications	R092670-PSY-3001	na	6963412	EDMS-PSDB-6963412	na
6/8/2007	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-3007	183	0183	GW eCTD TOC	na
6/14/2007	Protocol Amendment	na	New Protocol	R092670-PSY-1008	184	0184	GW eCTD TOC	na
6/15/2007	General Correspondence	na	IRB Waiver Request	R092670-PSY-1008	185	0185	GW eCTD TOC	na
6/15/2007	FDA Correspondence	na	Email: IND 67,356 3-Month Product Formulation: IND 76,952	na	na	na	06-15-07 Email	na
6/29/2007	FDA Correspondence	na	Letter: 06/07/07 Official Meeting Minutes	na	na	na	06-29-07 Letter	na
7/31/2007	Protocol Amendment	na	Change in Protocol	R092670-PSY-3006	186	0186	GW eSIG TOC	na
8/1/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3007	187	0187	GW eSIG TOC	na
8/13/2007	General Correspondence	na	Clarification of Official Minutes of the 07 June 2007 Meeting - CMC & Biopharmaceutics pre-NDA	na	188	0188	GW eSIG TOC	na
8/21/2007	Safety Report	na	DE-JNJFOC-20061200532 F-2	R076477-BIM-3004	189	0189	GW eSIG TOC	na
8/27/2007	General Correspondence	na	Sample Dataset Submission for IT Testing	na	190	0190	GW eSIG TOC	na
9/12/2007	FDA Correspondence	na	Email: Paliperidone palmitate NDA Submission Plans	na	na	na	09-12-07 Email	na
9/19/2007	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-1008	191	0191	GW eSIG TOC	na
9/20/2007	Annual Report	na	Reporting Period: 07/20/06 - 07/19/07	na	192	0192	GW eSIG TOC	na
11/1/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3007	193	0193	GW eSIG TOC	na
11/2/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3006	194	0194	GW eSIG TOC	na
11/29/2007	Safety Report	na	DE-JNJFOC-20061200532 F-3	R076477-BIM-3004	195	0195	GW eSIG TOC	na
12/6/2007	Record of Contact	6/16/2004	Minutes of June 16,2004 CMC/Biopharmaceutics End of Phase 2 Meeting for Paliperidon Palmitate	na	na	na	12-06-07 Email	na
12/11/2007	Information Amendment	na	CMC Drug Substance, Drug Product and Stability Data	na	196	0196	GW eSIG TOC	na
12/21/2007	General Correspondence	na	Request for Proposed Proprietary Name Review	na	197	0197	GW eSIG TOC	na
12/27/2007	Protocol Amendment	na	New Investigators	R092670-PSY-3006	198	0198	GW eSIG TOC	na
1/9/2008	Information Amendment	na	Pharmacology/Toxicology	na	199	0199	GW eSIG TOC	na
1/15/2008	Protocol Amendment	na	New Investigators	R092670-PSY-3007	200	0200	GW eSIG TOC	na
1/23/2008	Protocol Amendment	na	Statistical Analysis Plan for R092670-PSY-3007	R092670-PSY-3007	201	0201	GW eSIG TOC	na
1/25/2008	General Correspondence	na	Postmarketing Study Commitment Final Report: Developmental Toxicity Study in the Rat Final Report	na	202	0202	GW eSIG TOC	na
1/30/2008	FDA Correspondence	na	Email/Attachment: IRB Waiver Granted	na	na	na	01-30-08 Email	na
2/1/2008	Protocol Amendment	na	New Investigators	R092670-PSY-1008	203	0203	GW eSIG TOC	na

Date	Submission Type	Date of Contact	Description	Protocol #	SN#	EDMS or Sequence #	Hyperlink	Gateway Receipt
2/8/2008	FDA Correspondence	na	Fax: SN 0204	na	na	na	02-08-08 Fax	na
2/8/2008	Safety Report	na	RU-JNJFOC-20070701878 Initial	R092670-PSY-3007	204	0204	GW eSIG TOC	na
2/28/2008	Protocol Amendment	na	New Investigators	R092670-PSY-3006	205	0205	GW eSIG TOC	na
2/28/2008	Protocol Amendment	na	New Investigators	R092670-PSY-3007	206	0206	GW eSIG TOC	na
3/19/2008	Protocol Amendment	na	Change in Protocol; New Investigators	R092670-PSY-3006	207	0207	GW eSIG TOC	na
3/21/2008	Safety Report	na	US-JNJFOC-20070204832	R076477-SCA-3001	208	0208	GW eSIG TOC	na
4/9/2008	FDA Correspondence	na	Email: SN 201 Study R092670-PSY-3007 Statistical Analysis Plan	R092670-PSY-3007	na	na	04-09-08 Email	na
4/21/2008	Protocol Amendment	na	Change in Protocol	R092670-PSY-1008	209	0209	GW eSIG TOC	na
4/21/2008	Information Amendment	na	CMC	na	209	0209	GW eSIG TOC	na
4/28/2008	FDA Correspondence	na	Email/Attachment: Statistical Analysis Plan	R092670-PSY-3007	na	na	04-28-08 Email	na
7/14/2008	FDA Correspondence	na	Email/Attachments: Study Question	na	na	na	07-14-08 Email	na
7/25/2008	Safety Report	na	US-JNJFOC-20080704122 Initial	R076477-PSZ-3001	210	0210	GW eSIG TOC	na
8/1/2008	General Correspondence	na	Type B End-of-Phase 2/Pre-Phase 3 Meeting Request	na	211	0211	GW eSIG TOC	na
8/11/2008	Safety Report	na	IN-JNJFOC-20080704122 F-1	R076477-PSZ-3001	212	0212	GW eSIG TOC	na
8/25/2008	Safety Report	na	IN-JNJFOC-20080704122 F-1	R076477-PSZ-3001	213	0213	GW eSIG TOC	na
8/29/2008	General Correspondence	na	Briefing Package for 7 Oct 2008 Type B End-of-Phase 2/Pre-Phase 3 Meeting	na	214	0214	GW eSIG TOC	na
Note: Effective 09/01/08, emails and ROCs are only available electronically.								na
9/16/2008	Protocol Amendment	na	Change in Protocol	R092670-PSY-1008	215	0215	GW eSIG TOC	na
9/19/2008	Annual Report	na	Reporting Period: 07/20/07 - 07/19/08	na	216	0216	GW eSIG TOC	na
9/23/2008	Safety Report	na	IN-JNJFOC-20070201813 F-2	R076477-SCA-3002	217	0217	GW eSIG TOC	na
9/24/2008	General Correspondence	na	Updated Clinical Protocol Summary for 07Oct2008 Type C Meeting	na	218	0218	GW eSIG TOC	na
9/30/2008	FDA Correspondence	na	Preliminary Comments for Oct 7 Meeting	na	na	na	09-30-08 Email	na
10/16/2008	FDA Correspondence	na	Email/Attachments: Paliperidone palmitate Meeting Minutes	na	na	na	10-16-08 Email	na
10/31/2008	General Correspondence	na	Minutes of the 7Oct08 End of Phase 2/Pre-Phase 3 Mtg.	na	219	0219	GW eSIG TOC	na
11/6/2008	FDA Correspondence	na	Email/Attachment from FDA: PSP Issue Follow-up	na	na	na	11-06-08 Email	na
2/19/2009	Safety Report	na	DE-JNJFOC-20061200532 F-4	R076477-BIM-3004	220	0220	GW eSIG TOC	67356-0220_eSIG
3/4/2009	IND Amendment	na	Updated Investigator's Brochure, Edition 9, 02/25/08	na	221	0221	GW eSIG TOC	67356-0221_eSIG
4/13/2009	Protocol Amendment	na	New Protocol	R092670-SCH-3004	222	0222	GW eSIG TOC	67356-0222_eSIG
4/13/2009	General Correspondence	na	Justification for Suicidality Assessment	na	222	0222	GW eSIG TOC	67356-0222_eSIG
4/16/2009	Safety Report	na	PL-JNJFOC-20081000072 Initial 7-Day Report	R076477-PSZ-3002	223	0223	GW eSIG TOC	67356-0223_eSIG
4/22/2009	General Correspondence	na	Response Requested: Approval of Suicidality Assessment Plans for the Paliperidone Palmitate Development Programs and Approval to Use the ISST-Plus Scale	na	224	0224	GW eSIG TOC	67356-0224_eSIG
4/23/2009	FDA Correspondence	na	Email to FDA: Palmitate Suicide Assessment Plans	na	na	na	04-23-09 Email	na
4/29/2009	Safety Report	na	PL-JNJFOC-20081000072 F-1	R076477-PSZ-3002	225	0225	GW eSIG TOC	67356-0225_eSIG
6/2/2009	FDA Correspondence	na	FDA Letter: Suicide Assessment with ISST-plus	R092670-SCH-3004	na	na	06-02-09 Letter	na
6/9/2009	Protocol Amendment	na	New Investigators	R092670-PSY-3006	226	0226	GW eSIG TOC	67356-0226_eSIG
6/11/2009	Information Amendment	na	Chemistry, Manufacturing & Controls	R092670-SCH-3004	227	0227	GW eSIG TOC	67356-0227_eSIG

NDA 22-264 INVEGA SUSTENNA (paliperidone palmitate) (R092670) Long-Acting Injection (JNJ-16977831)

Date	Submission Type	Date of Contact	Description	Suppl#	EDMS or Sequence #	Hyperlink	Gateway Receipt
10/25/2007	Original NDA	na	Original New Drug Application	na	0000	GW eSIG TOC	na
10/26/2007	General Correspondence	na	Desk Copy - Review Aid	na	na	10-26-07 Desk Copy	na
11/7/2007	FDA Correspondence	na	Letter: NDA Receipt Acknowledgement	na	na	11-07-07 Letter	na
12/5/2007	FDA Correspondence	na	Email: Information Request	na	na	12-05-07 Email	na
12/7/2007	FDA Correspondence	na	Email/Attachment: Request for Datasets	na	na	12-07-07 Email	na
12/11/2007	NDA Amendment	na	Response to FDA Request for Carcinogenicity Tumor Dataset	na	0001	GW eSIG TOC	na
12/19/2008	FDA Correspondence	na	Email: 3-Month Pali Palmitate IND 76,952 Plans and NDA 22-264 Tradename Question	na	na	12-19-07 Email	na
12/21/2007	General Correspondence	na	Request for Proposed Proprietary Name Review	na	0002	GW eSIG TOC	na
12/21/2007	FDA Correspondence	na	Email/Attachment: Filing Communication Letter	na	na	12-21-07 Email	na
12/21/2007	FDA Correspondence	na	Letter: Filing Communication Letter	na	na	12-21-07 Letter	na
1/9/2008	General Correspondence	na	Response to FDA Filing Communication: Request for Carcinogenicity Data Variables	na	0003	GW eSIG TOC	na
1/10/2008	FDA Correspondence	na	Email/Attachment: Reformatted Tumor Dataset	na	na	01-10-08 Email	na
1/30/2008	FDA Correspondence	na	Email/Attachment: Review of the NDA	na	na	01-30-08 Email	na
2/7/2008	FDA Correspondence	na	Email: Dystonia Class Labeling Follow-up to Our Earlier Discussion	na	na	02-07-08 Email	na
2/11/2008	FDA Correspondence	na	Email/Attachment: RISPERDAL and INVEGA Clinical Development Program Analyses	na	na	02-11-08 Email	na
2/25/2008	Safety Update	na	4-Month Safety Update	na	0004	GW eSIG TOC	na
2/21/2008	General Correspondence	na	Response to FDA RFI: SAS Data Sets for Study R092670-PSY-3001	na	0005	GW eSIG TOC	na
2/25/2008	FDA Correspondence	na	Email/Attachments: 4-Month Safety Update-Response to Email Dated 14 Feb for SAS Data Sets	na	na	02-25-08 Email	na
2/27/2008	General Correspondence	na	Transfer of NDA Ownership	na	0006	GW eSIG TOC	na
2/27/2008	General Correspondence	na	Transfer of NDA Ownership	na	0007	GW eSIG TOC	na
3/21/2008	FDA Correspondence	na	Email/Attachment: Metabolic Parameter Request	na	na	03-21-08 Email	na
4/9/2008	FDA Correspondence	na	Email: Voice Mail Follow-up: Study R092670-PSY-3001	na	na	04-09-08 Email	na
4/22/2008	FDA Correspondence	na	Letter: Request for CMC Information	na	na	04-22-08 Letter	na
4/30/2008	FDA Correspondence	na	Email: CMC Questions	na	na	04-30-08 Email	na
5/2/2008	General Correspondence	na	Response to FDA RFI: Study Center Information	na	0008	GW eSIG TOC	na
5/12/2008	FDA Correspondence	na	Email: Request for Update on Information Request Response	na	na	05-12-08 Email	na
5/12/2008	General Correspondence	na	Response to FDA RFI: IVIVC Information	na	0009	GW eSIG TOC	na
5/13/2008	FDA Correspondence	na	Email: Follow-up Information on Study R076477-PSY-3001	na	na	05-13-08 Email	na
5/16/2008	FDA Correspondence	na	Email: Biopharmaceutics Telecon	na	na	05-16-08 Email	na
5/18/2008	FDA Correspondence	na	Email: CMC Response Timeline	na	na	05-18-08 Email	na
5/20/2008	FDA Correspondence	na	Letter: Comments Re: CMC Section of 10/25/07 Submission	na	na	05-20-08 Letter	na
5/21/2008	General Correspondence	na	Status of Ongoing Study R076477-PSY-3001, Pending NDA 22-264	na	0010	GW eSIG TOC	na
5/21/2008	General Correspondence	na	Desk Copy - Review Aid	na	na	05-21-08 Desk Copy	na
5/22/2008	FDA Correspondence	na	Email/Attachment: Biopharm Teleconference on 19 May 2008	na	na	05-22-08 Email	na
5/23/2008	FDA Correspondence	na	Email/Attachment: Biopharm Teleconference on 19 May 2008	na	na	05-23-08 Email	na
5/23/2008	FDA Correspondence	na	Email: Information Request	na	na	05-23-08 Email	na
5/27/2008	FDA Correspondence	na	Email: Receipt of Questions	na	na	05-27-08 Email	na
5/28/2008	General Correspondence	na	Minutes of 19 May 2008 Teleconference	na	0011	GW eSIG TOC	na
5/28/2008	General Correspondence	na	Response to FDA RFI: CMC Request of 22 April 2008	na	0012	GW eSIG TOC	na
6/2/2008	General Correspondence	na	Response to FDA RFI: Adverse Event Rates and Revised Table 1	na	0013	GW eSIG TOC	na
6/3/2008	General Correspondence	na	Response to FDA RFI: IVIVC Supporting Data and Computer Programs	na	0014	GW eSIG TOC	na
6/3/2008	FDA Correspondence	na	Email: FDA Request for Samples of Pali Palmitate Drug Product	na	na	06-03-08 Email	na

6/4/2008	FDA Correspondence	na	Email: DMF Request	na	na	06-04-08 Email	na
6/11/2008	FDA Correspondence	na	Email/Attachment: NDA 22-264 Proprietary Name Still Under Review	na	na	06-11-08 Email	na
6/13/2008	General Correspondence	na	Response to FDA RFI: CMC Request of 20 May 2008	na	0015	GW eSIG TOC	na
6/18/2008	FDA Correspondence	na	Email from FDA: Request Additional Information	na	na	06-16-08 Email	na
6/23/2008	FDA Correspondence	na	Email: Request for Phone/Fax Info	na	na	01-23-08 Email	na
6/23/2008	FDA Correspondence	na	Email: Peds Question	na	na	06-23-08 Email	na
6/23/2008	FDA Correspondence	na	Email: Additional Info Request (Clinical)	na	na	06-23-08 Email	na
6/23/2008	FDA Correspondence	na	Email: Update - R092670-PSY-3001, PSY-3002, & PSY-1004	na	na	06-23-08 Email	na
6/25/2008	FDA Correspondence	na	Email/Attachments: Response to RFI for Information: Investigator Glass	na	na	06-25-08 Email	na
6/25/2008	FDA Correspondence	na	Email/Attachment: Additional Info Request (Clinical)	na	na	06-25-08 Email	na
6/26/2008	FDA Correspondence	na	Email/Attachments: Response to RFI for Information: Investigator Chaganti	na	na	06-26-08 Email	na
6/26/2008	General Correspondence	na	Follow Up on Studies R092670-PSY-3001, R092670-PSY-3002, R092670-PSY-1004; Response Requested: for Revised R092670-PSY-3002 Report	na	0016	GW eSIG TOC	na
6/27/2008	FDA Correspondence	na	Email: Pediatric Study Requirements	na	na	06-27-08 Email	na
6/30/2008	Record of Contact	6/30/2008	Summary of 30 June 2008 FDA/J&JPRD Telecon - CMC	na	8615438	06-30-08 ROC	na
7/2/2008	NDA Amendment	na	Request for FDA to Review Information for Use Leaflet & Packaging Color Scheme	na	0017	GW eSIG TOC	na
7/2/2008	FDA Correspondence	na	Email/Attachment: Request Additional Information	na	na	07-02-08 Email	na
7/2/2008	FDA Correspondence	na	Email/Attachments: Summary of 30June2008 Telecon: DMF 20902 and NDA 22-264 and Available Responses to Questions	na	na	07-02-08 Email	na
7/10/2008	FDA Correspondence	na	Email: Addition of "crude" for Identification and CMC RA Responsibility Change	na	na	07-10-08 Email	na
7/11/2008	General Correspondence	na	Response to RFI: CMC Request of 30 June 2008	na	0018	GW eSIG TOC	na
7/11/2008	FDA Correspondence	na	Email/Attachments: Status of Data QC Review - Summary Table	na	na	07-11-08 Email	na
7/15/2008	General Correspondence	na	Response to FDA RFI: Pediatric Waiver Request	na	0019	GW eSIG TOC	na
7/15/2008	General Correspondence	na	Follow-up Information on Study R092670-PSY-1004; Agreement for Data Erratum to Clinical Study Report R092670-PSY-1004	na	0020	GW eSIG TOC	na
7/29/2008	FDA Correspondence	na	Email: Information Request - Receipt of Questions	na	na	07-29-08 Email	na
7/29/2008	FDA Correspondence	na	Letter: Information Request: CMC	na	na	07-29-08 Letter	na
8/12/2008	General Correspondence	na	Response to FDA RFI: CMC Request of 29 July 2008	na	0021	GW eSIG TOC	na
8/15/2008	FDA Correspondence	na	Email: Clinical Information Request	na	na	08-15-08 Email	na
8/15/2008	FDA Correspondence	na	Email/Attachment: Clinical Information Request	na	na	08-15-08 Email	na
8/20/2008	General Correspondence	na	Response to FDA RFI: Package Insert and Adverse Events in Acute Studies	na	0022	GW eSIG TOC	na
8/21/2008	FDA Correspondence	na	Email: Non-Objection to Amended CSR Approach for R076477-PSY-3001 and R092670-PSY-3002	na	na	08-21-08 Email	na
8/21/2008	FDA Correspondence	na	Email: Trademark Name INVEGA SUSTENNA Is Acceptable	na	na	08-21-08 Email	na
8/25/2008	FDA Correspondence	na	Letter: NDA Cannot Approve Letter	na	na	08-25-08 Letter	na
8/26/2008	FDA Correspondence	na	Email/Attachment: Action Letter	na	na	08-26-08 Email	na
Note: Effective 09/01/08, emails and ROCs are only available electronically.							na
9/2/2008	FDA Correspondence	na	Email: Action Letter	na	na	09-02-08 Email	na
9/16/2008	General Correspondence	na	Request for Meeting: Type A Meeting: Resubmission Contents to Address FDA's Complete Response Letter	na	0023	GW eSIG TOC	na
9/26/2008	FDA Correspondence	na	Email: Type B Meeting Request Granted for 11/21/08	na	na	09-26-08 Email	na
10/21/2008	General Correspondence	na	Background Briefing Package for 21 Nov 2008 Type B Meeting	na	0024	GW eSIG TOC	na
12/1/2008	FDA Correspondence	na	Email/Attached Letter: 11/21/08 Meeting Minutes	na	na	12-01-08 Email	na
1/13/2009	General Correspondence	na	Sponsor's Minutes from the 21Nov2008 NDA Resubmission Meeting	na	0025	GW eSIG TOC	22264-0025_eSIG

2/3/2009	General Correspondence	na	Resubmission: Sponsor's Responses to FDA's Complete Response Letter	na	0026	GW eSIG TOC	22264-0026_eSIG
2/6/2009	FDA Correspondence	na	Email from FDA: Tradename Submission	na	na	02-06-09 Email	na
2/11/2009	Other	na	Request for Proprietary Name Review: Re-review of Previous Tentatively Approved Proprietary Name	na	0027	GW eSIG TOC	22264-0027_eSIG
2/13/2009	FDA Correspondence	na	Email/Attachment from FDA: 2/2/09 Submission is a Class 2 Resubmission with a 6 Month Review Cycle	na	na	02-13-09 Email	na
2/13/2009	FDA Correspondence	na	FDA Letter: 02/03/09 Submission Receipt Acknowledgement	na	na	02-13-09 Letter	na
2/24/2009	General Correspondence	na	Response to Request for Information: CMC Drug Substance	na	0028	GW eSIG TOC	22264-0028_eSIG
3/24/2009	Other	na	Certification for Delay of Posting Clinical Trial Results on www.ClinicalTrials.gov	na	0029	GW eCTD TOC	22264-0029_eSIG
3/30/2009	FDA Correspondence	na	Email from FDA: RFI - DMF 20902 Vacuum Leak Test Method	na	na	03-30-09 Email	na
4/3/2009	FDA Correspondence	na	Email/Attachments to FDA: DMF 20902 Response to Request from 03/30/09	na	na	04-03-09 Email	na
4/24/2009	FDA Correspondence	na	FDA Letter: CMC Reviewer RFI	na	na	04-24-09 Letter	na
5/1/2009	FDA Correspondence	na	Email from FDA: DMF 20902 Amendment - Additional Stability Data Included for Cork	na	na	05-01-09 Email	na
5/5/2009	FDA Correspondence	na	Email from FDA: Review Team RFI - "Mock-up" Copy of Proposed Syringe and Carton Kit	na	na	05-05-09 Email	na
5/7/2009	General Correspondence	na	Pre-Launch Activities Importation Request	na	0030	GW eSIG TOC	22264-0030_eSIG
5/8/2009	FDA Correspondence	na	Email/Attachments to FDA: Pre-Launch Activities Importation Request	na	na	05-08-09 Email	na
5/14/2009	FDA Correspondence	na	Email to FDA: Mock-ups of INVEGA SUSTENNA Commercial Product	na	na	05-14-09 Email	na
5/15/2009	General Correspondence	na	Response to RFI: Clinical Study Report PALIOROS-PSZ-1001	na	0031	GW eSIG TOC	22264-0031_eSIG
5/15/2009	FDA Correspondence	na	Email to FDA: Information Request	na	na	05-15-09 Email	na
5/15/2009	FDA Correspondence	na	FDA Letter: Proposed Proprietary Name, INVEGA SUSTENNA, Acceptable	na	na	05-15-09 Letter	na
5/18/2009	FDA Correspondence	na	Email/Attachment to FDA: Information Request - Xu et.al Publication	na	na	05-18-09 Email	na
5/20/2009	General Correspondence	na	Response to RFI: Efficacy Subgroup Analyses for R092670-PSY-3007	na	0032	GW eSIG TOC	22264-0032_eSIG
5/20/2009	FDA Correspondence	na	Email/Attachments: Information Request	na	na	05-20-09 Email	na
5/22/2009	General Correspondence	na	Responst to RFI: CM&C Response to Information Request Letter of 23 April 2009	na	0033	GW eSIG TOC	22264-0033_eSIG
5/25/2009	General Correspondence	na	Response to RFI: SAS Programs for PSP Analyses	na	na	05-25-09 Gen Corr	na
5/26/2009	FDA Correspondence	na	Email/Attachment to FDA: SAS Code for PSP Analyses - Information Request for NDA 22-264	na	na	05-26-09 Email	na
5/27/2009	FDA Correspondence	na	Email to FDA: Mock-ups - RE: SAS Code for PSP Analysis - Information Request for NDA 22-264	na	na	05-27-09 Email	na
6/1/2009	FDA Correspondence	na	Email from FDA: Request for Information - Liver Enzymes	na	na	06-01-09 Email	na
6/4/2009	FDA Correspondence	na	Email from FDA: Information Request for Additional Financial Disclosure Information	na	na	06-04-09 Email	na
6/5/2009	FDA Correspondence	na	Email/Attachment to FDA: Response to Request for Location of Narratives for Elevated Liver Enzymes	na	na	06-05-09 Email	na
6/8/2009	FDA Correspondence	na	Email/Attachments to FDA: Janssen Pharmaceutica N.V. Samples to FDA	na	na	06-08-09 Email	na
6/8/2009	FDA Correspondence	na	Email from FDA: Re: Janssen Pharmaceutica N.V. Samples to FDA	na	na	06-08-09 Email	na
6/9/2009	Other	na	Pre-Launch Activities Importation Request Amendment	na	0034	GW eSIG TOC	22264-0034_eSIG
6/11/2009	FDA Correspondence	na	Email/Attachment to FDA: UPS Tracking Numbers for Samples	na	na	06-11-09 Email	na
6/15/2009	FDA Correspondence	na	Email from FDA: Information Request (Simulation Code and Dataset)	na	na	06-15-09 Email	na
6/15/2009	FDA Correspondence	na	Email to FDA: Information Request (Simulation Code and Dataset)	na	na	06-15-09 Email	na
6/16/2009	FDA Correspondence	na	Email from FDA: Information Request (Simulation Code and Dataset)	na	na	06-16-09 Email	na

6/16/2009	FDA Correspondence	na	Email/Attachments to FDA: Amended PLAIR - NDA 22-264 Pre-Launch Activities Importation Request	na	na	06-16-09 Email	na
6/16/2009	FDA Correspondence	na	Email/Attachment to FDA: Amended PLAIR - NDA 22-264 Pre-Launch Activities Importation Request Response	na	na	06-16-09 Email	na
6/16/2009	FDA Correspondence	na	Email to FDA: Information Request (Simulation Code and Dataset) Update	na	na	06-16-09 Email	na
6/19/2009	FDA Correspondence	na	Email/Attachments from FDA: Amended PLAIR is Acceptable	na	na	06-19-09 Email	na
6/22/2009	Amendment to Pending Application	na	Response to RFI: Data Files and Control Script Files Used to Conduct Simulations	na	0035	GW eSIG TOC	22264-0035_eSIG
6/22/2009	Amendment to Pending Application	na	Response to RFI: Financial Disclosure Clinical Investigators	na	0036	GW eSIG TOC	22264-0036_eSIG
6/22/2009	FDA Correspondence	na	Email/Attachments to FDA: Response to RFI: Data Sets and Financial Disclosures	na	na	06-22-09 Email	na
6/24/2009	FDA Correspondence	na	Email from FDA: Pediatric Plan Request	na	na	06-24-09 Email	na
6/24/2009	FDA Correspondence	na	Email/Attachment from FDA: Pediatric Plan	na	na	06-24-09 Email	na
6/25/2009	Amendment to Pending Application	na	Response to RFI: Proposed Pediatric Development Plan	na	0037	GW eSIG TOC	22264-0037_eSIG
6/25/2009	FDA Correspondence	na	Email/Attachments to FDA: Pediatric Plan Request	na	na	06-25-09 Email	na
7/1/2009	FDA Correspondence	na	Email/Attachments to FDA: Drug Listing for Unapproved Product for Pre-Launch Activities Importation Request	na	na	07-01-09 Email	na
7/2/2009	FDA Correspondence	na	Email/Attachments to FDA: Pre-Launch Activities Importation Request	na	na	07-02-09 Email	na
7/1/2009	FDA Correspondence	na	Email to FDA: RE: Drug Listing for Unapproved Product for Pre-Launch Activities Importation Request	na	na	07-01-09 Email	na
7/8/2009	FDA Correspondence	na	Fax from FDA: CMC Information Request Letter	na	na	07-08-09 Fax	na
7/8/2009	FDA Correspondence	na	Letter from FDA: CMC Information Request Letter	na	na	07-08-09 Letter	na
7/8/2009	FDA Correspondence	na	Email to FDA: Second Shipment RE: Amended PLAIR - NDA 22-264 Pre-Launch Activites Importation Request	na	na	07-08-09 Email	na
7/9/2009	FDA Correspondence	na	Email to FDA: Response to Informatioin Request	na	na	07-07-09 Email	na
7/10/2009	Amendment to Pending Application	na	Response to RFI: CMC Drug Substance Specifications	na	0038	GW eSIG TOC	22264-0038_eSIG
7/12/2009	FDA Correspondence	na	Email/Attachment from FDA: Revised Labeling	na	na	07-12-09 Email	na
7/14/2009	FDA Correspondence	na	Email/Attachment from FDA: Container/Carton Labeling	na	na	07-14-09 Email	na
7/14/2009	FDA Correspondence	na	Letter from FDA: Container/Carton Labeling	na	na	07-14-09 Letter	na
7/15/2009	FDA Correspondence	na	Email from FDA: Postmarketing Requirements/Postmarketing Commitments	na	na	07-15-09 Email	na
7/16/2009	FDA Correspondence	na	Email from FDA: List of Attendees for 07/17/09 Telecon	na	na	07-16-09 Email	na
7/16/2009	Other	na	Response to RFI: CMC Drug Product Specifications	na	0039	GW eSIG TOC	22264-0039_eSIG
7/16/2009	FDA Correspondence	na	Email to FDA: 07/17/09 Telecon Call-in Number and List of JJPRD Attendees	na	na	07-16-09 Email	na
7/16/2009	FDA Correspondence	na	Email to FDA: Postmarketing Requirements/Postmarketing Commitments	na	na	07-16-09 Email	na
7/17/2009	Amendment to Pending Application	na	Response to RFI: Draft Labeling	na	0040	GW eSIG TOC	22264-0040_eSIG
7/20/2009	Amendment to Pending Application	na	Response to RFI: Post Marketing Commitments	na	0041	GW eSIG TOC	22264-0041_eSIG
7/21/2009	FDA Correspondence	na	Email/Attachment from FDA: Revised Labeling (#2)	na	na	07-21-09 Email	na
7/21/2009	FDA Correspondence	na	Email to FDA: Attached Listing of Discontinuations for AEs with Request	na	na	07-21-09 Email	na
7/21/2009	FDA Correspondence	na	Email/Attachments to FDA: Response for PMC	na	na	07-21-09 Email	na
7/22/2009	FDA Correspondence	na	Email to FDA: Response for PMC - One More Publication Cited to Send	na	na	07-22-09 Email	na
7/22/2009	FDA Correspondence	na	Email from FDA: Division Meeting to Discuss PMC on 23 July 2009	na	na	07-22-09 Email	na

7/22/2009	FDA Correspondence	na	Email/Attachments to FDA: Revised Draft Labeling - Clean and Marked	na	na	07-22-09 Email	na
7/22/2009	FDA Correspondence	na	Email/Attachment to FDA: Response for PMC - Additional Publication	na	na	07-22-09 Email	na
7/23/2009	FDA Correspondence	na	Email/Attachments to FD: Revised Draft Label	na	na	07-23-09 Email	na
7/23/2009	FDA Correspondence	na	Email/Attachments to FDA: Response to Packaging Components	na	na	07-23-09 Email	na
7/23/2009	Amendment to Pending Application	na	Response to Request for Information and Waiver Request: Draft Labeling and Waiver Request under 21 CFR 201.58	na	0042	GW eSIG TOC	22264-0042_eSIG
7/23/2009	Amendment to Pending Application	na	Response to RFI: Labels and Labeling	na	0043	GW eSIG TOC	22264-0043_eSIG
7/28/2009	FDA Correspondence	na	Email/Attachment from FDA: Revised Package Insert for Paliperidone Palmitate	na	na	07-28-09 Email	na
7/28/2009	FDA Correspondence	na	Email from FDA: Comments Regarding Carton/Container Labeling with Request for Agreement	na	na	07-28-09 Email	na
7/28/2009	FDA Correspondence	na	Email/Attachments to FDA: Response to Draft Labeling T-con Call In Information	na	na	07-28-09 Email	na
7/29/2009	FDA Correspondence	na	Email from FDA: Response to Draft Labeling T-con Call In Information	na	na	07-29-09 Email	na
7/29/2009	FDA Correspondence	na	Email/Attachment from FDA: USPI Label with Comment in Section 6.4	na	na	07-29-09 Email	na
7/29/2009	FDA Correspondence	na	Email/Attachment to FDA: PI Comments and Edits	na	na	07-29-09 Email	na
7/29/2009	FDA Correspondence	na	Email from FDA: Carton/Container Requested Changes Proposal is Acceptable	na	na	07-29-09 Email	na
7/29/2009	FDA Correspondence	na	Email to FDA: PI Comment	na	na	07-29-09 Email	na
7/29/2009	FDA Correspondence	na	Email/Attachments from FDA: Label and PPI	na	na	07-29-09 Email	na
7/30/2009	FDA Correspondence	na	Email/Attachments to FDA: Label and PPI	na	na	07-30-09 Email	na
7/31/2009	FDA Correspondence	na	Email to FDA: Posting of a PI on FDA Web Page	na	na	07-31-09 Email	na
7/31/2009	FDA Correspondence	na	Email/Attachment from FDA: comments re: Posting of a PI on FDA Web Page and NDA Approval Letter	na	na	07-31-09 Email	na
8/3/2009	FDA Correspondence	na	Email to FDA: FPL and SPL Submission to Contain Correct TOC	na	na	08-03-09 Email	na
8/3/2009	FDA Correspondence	na	Email from FDA: Posting of a PI on FDA Web Page Correction Acknowledgement	na	na	08-03-09 Email	na
8/3/2009	Advertising	na	01PM09005	na	na	eSub TOC	na

Exhibit 9

STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,254,556

Issued: October 19, 1993
Expiration Date: October 27, 2009

Inventors: Cornelus G.M. Janssen, Alfonsus G. Knaeps, Ludo E. J. Kennis, and Jan Vandenberk

Title: 3-PIPERIDINYL-1,2-BENZISOXAZOLES

Statement of Eligibility for Extension of Patent Term Due to Regulatory Review

I, Hal Brent Woodrow, represent that I am the attorney of record duly appointed by the assignee of the entire right, title and interest in the patent application identified above, and do state on behalf of the Applicant as follows:

To the best of my knowledge, U.S. Patent No. 5,254,556 (the '556 Patent) meets all of the eligibility criteria set forth in 37 C.F.R §§1.710 and 1.720 for extension of patent term.

The '556 Patent claims a "product" as that term is defined in 37 C.F.R §1.710, specifically the composition and use of a new human drug, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension 37 C.F.R §1.720(a).

The term of the '556 Patent has never been previously extended. 37 C.F.R §1.720(b).

An application for extension of the term of the '556 Patent in compliance with 37 C.F.R §1.740 is herewith submitted. 37 C.F.R §1.720(c).

The approved product, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, has been subject to a regulatory review period before its commercial marketing or use as defined in 35 U.S.C. §156(g). 37 C.F.R §1.720(d).

The approved product, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, has received permission for commercial marketing or use and the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred. 37 C.F.R §1.720(e).

The application for extension of the term of the '556 Patent submitted herewith is submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred. 37 C.F.R §1.720(f).

The term of the '556 Patent, including any interim extension issued pursuant to § 1.790, has not expired before the submission of an application in compliance with 37 C.F.R. § 1.741. 37 C.F.R §1.720(g).

No other patent term has been extended for the same regulatory review period for the approved product, INVEGA SUSTENNA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, 37 C.F.R §1.720(h).

The extension claimed is 1449 days, setting the patent to expire on October 15, 2013. The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase began on June 2, 2003 (the effective date of the IND) and ended on October 26, 2007 (submission date of the NDA).

(2) The approval phase began on October 26, 2007 (day of receipt by the FDA of the NDA) and approval was granted on July 31, 2009.

(3) The total number of days in the testing phase (from and including June 2, 2003 to and including October 26, 2007) is 1608 days from the start date to the end date, end date included. One half of the testing phase is 804 days.

(4) The total number of days in the approval phase is (from and including October 26, 2007 to and including July 31, 2009) is 645 days from the start date to the end date, end date included.

(5) The patent issued on October 19, 1993 before the regulatory approval process began.

(6) Applicant acted with due diligence throughout the entire regulatory review period.

(7) The sum of the (a) number of days in one half of the testing phase (804), and (b) number of days in the approval phase (645) is: 1449.

(8) The original expiration date of the patent is October 27, 2009.

(9) Addition of the extension of 1449 days to the original expiration date of the patent extends the expiration date of the patent to October 15, 2013.

(10) Fourteen years from the approval date of the product (July 31, 2009) is July 31, 2023.

(11) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 1449 days sets the patent to expire on October 15, 2013, which is before the date that is 14 years post-approval (July 31, 2023).

(12) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the extension of 1449 days patent is less than five years.

(13) In light of the conclusions set forth above, the extended expiration date of the '556 Patent is believed to be October 15, 2013.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment,

or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 5 August 2009

Hal Brent Woodrow, Reg. No. 32,501

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